1. Document ID: US 6214821 B1

L8: Entry 1 of 52

File: USPT

Apr 10, 2001

US-PAT-NO: 6214821
DOCUMENT-IDENTIFIER: US 6214821 B1
TITLE: Methods and composition for the inhibition of cancer cells
DATE-ISSUED: April 10, 2001

US-CL-CURRENT: 514/214.02; 514/283

APPL-NO: 9/ 262452
DATE FILED: March 4, 1999

PARENT-CASE:
This application claims the benefit of U.S. Provisional Application No. 60/076,960 filed Mar. 5, 1998.

AB: Pharmaceutical compositions comprising a topoisomerase I inhibitor, such as camptothecin or a camptothecin analog, and a staurosporine such as 7-hydroxystaurosporine, together with a pharmaceutically acceptable carrier or diluent are provided. In other aspects, methods of inhibiting the growth of cancer cells are provided by contacting the cells with an cell growth inhibiting amount of a topoisomerase I inhibitor, such as camptothecin or a camptothecin analog, and a staurosporine, such as 7-hydroxystaurosporine, while protecting normal cells from topoisomerase I inhibitor induced cytotoxicity.

IN: Daoud; Sayed S.

2. Document ID: US 6210939 B1

L8: Entry 2 of 52

File: USPT

Apr 3, 2001

US-PAT-NO: 6210939
DOCUMENT-IDENTIFIER: US 6210939 B1
TITLE: Recombinant adenoviral vector and methods of use
DATE-ISSUED: April 3, 2001

US-CL-CURRENT: 435/252.3, 435/320.1, 435/363, 435/366, 435/370, 435/371

APPL-NO: 8/ 328673
DATE FILED: October 25, 1994

PARENT-CASE:
This application is a continuation-in-part of U.S. Ser. No. 08/233,777, filed May 19, 1994, now abandoned which is a continuation-in-part of U.S. Ser. No. 08/142,669 filed Oct. 25, 1993, now abandoned the contents of which are hereby incorporated by reference into the present disclosure.

AB: This invention provides a recombinant adenovirus expression vector characterized by the partial or total deletion of the adenoviral protein IX DNA and having a gene encoding a foreign protein or a functional fragment or mutant thereof. Transformed host cells and a method of producing recombinant proteins and gene therapy also are included within the scope of this invention. Thus, for example, the adenoviral vector of this invention can contain a foreign gene for the expression of a protein effective in regulating the cell cycle, such as p53, Rb, or mitosin, or in inducing cell death, such as the conditional suicide gene thymidine kinase. (The latter must be used in conjunction with a thymidine kinase metabolite in order to be effective).

IN: Gregory; Richard J., Wills; Ken N., Maneval; Daniel C.

3. Document ID: US 6187587 B1

L8: Entry 3 of 52

File: USPT

Feb 13, 2001

US-PAT-NO: 6187587
DOCUMENT-IDENTIFIER: US 6187587 B1
TITLE: Antisense inhibition of e2f transcription factor 1 expression
DATE-ISSUED: February 13, 2001

US-CL-CURRENT: 435/375; 435/325, 435/6, 435/91.1, 536/23.1, 536/24.3, 536/24.31, 536/24.33, 536/24.5

APPL-NO: 9/ 517584
DATE FILED: March 2, 2000

AB: Antisense compounds, compositions and methods are provided for modulating the expression of E2F transcription factor 1. The compositions comprise antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding E2F transcription factor 1. Methods of using these compounds for modulation of E2F transcription factor 1 expression and for treatment of diseases associated with expression of E2F transcription factor 1 are provided.

IN: Popoff; Ian, Brown-Driver; Vickie L., Cowsert; Lex M.

4. Document ID: US 6169073 B1

L8: Entry 4 of 52

File: USPT

Jan 2, 2001

US-PAT-NO: 6169073
DOCUMENT-IDENTIFIER: US 6169073 B1
TITLE: Peptides and peptidomimetics with structural similarity to human p53 that activate p53 function
DATE-ISSUED: January 2, 2001

US-CL-CURRENT: 514/12; 530/300, 530/317, 530/323, 530/324

APPL-NO: 8/ 392542
DATE FILED: February 16, 1995

AB: The present invention provides peptides and peptidomimetics corresponding to part
or to the entirety of the region encompassed by residues 360-386 of human p53, said peptides
and peptidomimetics characterized by the ability to activate DNA binding of wild-type p53
and of select tumor-derived p53 mutants. Pharmaceutical compositions of the compounds of the
invention and methods of using these compositions therapeutically are also provided.

IN: Halazonetis; Thanos, Hartwig; Wolfgang

5. Document ID: US 6153391 A

L8: Entry 5 of 52

File: USPT

Nov 28, 2000

US-PAT-NO: 6153391
DOCUMENT-IDENTIFIER: US 6153391 A
TITLE: Interruption of binding of MDM2 and P53 protein and therapeutic application thereof
DATE-ISSUED: November 28, 2000

US-CL-CURRENT: 435/7.1; 514/12, 514/13, 514/14, 514/15, 514/16, 514/17, 530/317, 530/324,
530/325, 530/326, 530/328, 530/329, 530/330

APPL-NO: 9/ 035686
DATE FILED: March 5, 1998

PARENT-CASE:
This is a division of application Ser. No. 08/424,957 filed Apr. 19, 1995, now U.S. Pat. No.
5,770,377, issued Jun. 23, 1998, which was a continuation-in-part of application Ser. No.
08/277,660, filed Jul. 20, 1994, now U.S. Pat. No. 5,702,908.

AB: A method for interfering with the binding between p53 and MDM2 or a protein
having a p53 binding site analogous to that of MDM2, which method comprises administering a
effective amount of a compound, selected from the group consisting of a peptide having up to
twenty eight amino acids which is able to disrupt or prevent binding between p53 and MDM2,
or a functional peptide analogue thereof., Compounds for use in the method, methods for
detecting such compounds and their application in the diagnosis and treatment of tumors is
also described and claimed.

IN: Picksley; Steven Michael, Lane; David Philip

6. Document ID: US 6149945 A

L8: Entry 6 of 52

File: USPT

Nov 21, 2000

US-PAT-NO: 6149945
DOCUMENT-IDENTIFIER: US 6149945 A
TITLE: Human fibroblast diffusable factors
DATE-ISSUED: November 21, 2000

US-CL-CURRENT: 424/520; 435/173.1

APPL-NO: 8/ 910544
DATE FILED: July 23, 1997

PARENT-CASE:
This is a continuation in part of U.S. application Ser. No. 08/407,883, filed Mar. 20, 1995, now
abandoned which is herein incorporated by reference.

AB: The present invention provides for numerous cell factors involved in a novel
cellular pathway that is activated in response to ionizing radiation. Several cell factor
activities are described which either complement the radioresistant DNA synthesis phenotype
of Ataxia Telangiectasia cells, or inhibit DNA synthesis in the cell. Other cell factor
activities are described which inhibit mitosis by arresting the cell cycle prior to cell
division. It is contemplated that compositions comprising the subject factors will be useful
as both research tools, and as therapeutic agents.

IN: Mirzayans; Razmik, Paterson; Malcolm C.

7. Document ID: US 6147056 A

L8: Entry 7 of 52

File: USPT

Nov 14, 2000

US-PAT-NO: 6147056
DOCUMENT-IDENTIFIER: US 6147056 A
TITLE: Use of locally applied DNA fragments
DATE-ISSUED: November 14, 2000

US-CL-CURRENT: 514/44; 424/450, 514/43, 514/45, 514/46, 514/47

APPL-NO: 9/ 048927
DATE FILED: March 26, 1998

PARENT-CASE:
RELATED APPLICATION(S) This application is a Continuation-in-Part of U.S. National Phase of
PCT/US96/08386 filed Jun. 3, 1996, and assigned U.S. application Ser. No. 08/952,697, filed Dec.
6, 1997, which is a Continuation-in-Part of application Ser. No. 08/467,012 filed Jun. 6, 1995,
now U.S. Pat. No. 5,955,059 the entire teachings of which are incorporated herein by reference.

AB: Methods of treatment or prevention of hyperproliferative diseases or
pre-cancerous conditions affecting epithelial cells, such as psoriasis, vitiligo, atopic
dermatitis, or hyperproliferative or UV-responsive dermatoses, hyperproliferative or
allergically mediated diseases of other epithelia and methods for reducing photoaging or for

prophylaxis against or reduction in the likelihood of the development of skin cancer, are
disclosed.

IN: Gilchrest; Barbara A., Yaar; Mina, Eller; Mark

8. Document ID: US 6140058 A

L8: Entry 8 of 52 File: USPT Oct 31, 2000

US-PAT-NO: 6140058
DOCUMENT-IDENTIFIER: US 6140058 A
TITLE: Activation of p53 protein
DATE-ISSUED: October 31, 2000

US-CL-CURRENT: 435/7.1; 424/155.1, 424/174.1, 435/7.23, 530/350, 530/358

APPL-NO: 8/ 446668
DATE FILED: July 24, 1995

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	9224784	November 26, 1992

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/GB93/02438	November 26, 1993	WO94/12202	Jun 9, 1994	Jul 24, 1995	Jul 24, 1995

AB: A class of mutant forms of p53 protein, such as His273 and Lys285, which are
defective in conversion from the latent to the activated state by casein kinase II, but with
the ability to be activated for specific DNA binding by the action of ligands such as
monoclonal antibody PAb421 and heat shock protein DnaK. Activation of these mutants, which
are found at high levels in certain types of tumour, can potentially lead to selective
growth arrest and induction of apoptosis in the tumor cells. p53 can be constitutively
activated also by deletion of the C-terminal 30 amino acids. p53 activated in this way, or
by ligand binding, can be administered for the purposes of tumour or cell growth
suppression.

IN: Lane; David Philip, Hupp; Theodore Robert

9. Document ID: US 6100243 A

L8: Entry 9 of 52 File: USPT Aug 8, 2000

US-PAT-NO: 6100243
DOCUMENT-IDENTIFIER: US 6100243 A
TITLE: Method of sensitizing tumor cells with adenovirus E1A
DATE-ISSUED: August 8, 2000

US-CL-CURRENT: 514/44; 424/93.21, 435/320.1, 435/455, 435/458, 435/69.1

APPL-NO: 8/ 853831
DATE FILED: May 9, 1997

PARENT-CASE:
This application is a continuation of application Ser. No. 08/301,316, filed Sep. 6, 1994, now
U.S. Pat. No. 5,776,743.

AB: The present invention is directed to methods of sensitizing a human tumor cell
with adenovirus E1A. The methods involve treating a human tumor cell by, first, introducing
into the tumor cell nucleic acid encoding a polypeptide having adenovirus E1A activity,
expressing the E1A active polypeptide in the cell, and then either contacting the E1A
expressing tumor cell with a chemotherapeutic agent or irradiating the E1A-expressing tumor
cell. The invention also provides methods of enhancing a subject's response to chemotherapy
or irradiation by introducing into a subject's tumor cells nucleic acid encoding a
polypeptide having adenovirus E1A activity, expressing the E1A active polypeptide in the
cells and finally, administering either a chemotherapeutic agent or irradiation. The
invention also provides a method of treating cancer.

IN: Frisch; Steven M.

10. Document ID: US 6096539 A

L8: Entry 10 of 52 File: USPT Aug 1, 2000

US-PAT-NO: 6096539
DOCUMENT-IDENTIFIER: US 6096539 A
TITLE: Protein activator of apoptosis
DATE-ISSUED: August 1, 2000

US-CL-CURRENT: 435/325; 435/320.1, 435/6, 536/23.1, 536/23.5, 536/24.3, 536/24.31, 536/24.33

APPL-NO: 9/ 329418
DATE FILED: June 10, 1999

AB: An isolated and purified human protein activator of apoptosis is described. A

cDNA sequence which encodes the native kinase of death is disclosed as well as the
structural coding region and the amino acid residue sequence. Methods are provided which
employ the sequences to identify compounds that modulate the biological and/or
pharmacological activity of the activator and hence regulate apoptosis.
Biologically-effective antisense molecules, as well as dominant negative mutant versions of
the apoptosis activator are described which are suitable for therapeutic use. The invention
is also drawn toward the study, prevention, diagnosis, and treatment of pathophysiological
disorders related to apoptosis.

IN: Gomes; Bruce Charles, Kasof; Garrett M., Prosser; Judith Caroline

APPL-NO: 8/ 442581
DATE FILED: May 16, 1995

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application is a continuation-in-part of U.S.
application Ser. No. 08/330,525, filed Oct. 28, 1994, now abandoned, the contents of which are
incorporated herein by reference.

AB: Disclosed herein are boronic ester and acid compounds, their synthesis and uses.
More specifically, disclosed herein is a method for reducing the rate of degradation of
proteins in an animal comprising contacting cells of the animal with certain boronic ester
and acid compounds.

IN: Adams; Julian, Ma; Yu-Ting, Stein; Ross, Baevsky; Matthew, Grenier; Louis,
Plamondon; Louis

11. Document ID: US 6090539 A

L8: Entry 11 of 52
File: USPT
Jul 18, 2000

US-PAT-NO: 6090539
DOCUMENT-IDENTIFIER: US 6090539 A
TITLE: Methods and compositions utilizing Rad51
DATE-ISSUED: July 18, 2000

US-CL-CURRENT: 435/4; 435/6

APPL-NO: 9/ 007020
DATE FILED: January 14, 1998

PARENT-CASE:
This Application claims benefit of 60/035,834, filed Jan. 30, 1997 and 60/045,668, filed May 6,
1997, both of which are expressly incorporated by reference herein.

AB: Compositions and methods are provided for identifying agents which bind to or
modulate Rad51.

IN: Haaf; Thomas, Golub; Efim Ilya, Reddy; Gurucharan, Radding; Charles Meyer, Ward;
David C.

12. Document ID: US 6083903 A

L8: Entry 12 of 52
File: USPT
Jul 4, 2000

US-PAT-NO: 6083903
DOCUMENT-IDENTIFIER: US 6083903 A
TITLE: Boronic ester and acid compounds, synthesis and uses
DATE-ISSUED: July 4, 2000

US-CL-CURRENT: 514/2; 514/64, 544/69, 546/13, 548/110, 548/405, 549/213, 549/4

13. Document ID: US 6069134 A

L8: Entry 13 of 52
File: USPT
May 30, 2000

US-PAT-NO: 6069134
DOCUMENT-IDENTIFIER: US 6069134 A
TITLE: Methods and compositions comprising DNA damaging agents and p53
DATE-ISSUED: May 30, 2000

US-CL-CURRENT: 514/44; 424/93.21, 435/320.1, 435/325, 435/455, 435/458, 435/69.1

APPL-NO: 8/ 953290
DATE FILED: October 17, 1997

PARENT-CASE:
This is a divisional application of Ser. No. 08/233,002 filed Apr. 25, 1994, now U.S. Pat. No.
5,747,469, issued May 5, 1998.

AB: The present invention relates to the use of tumor suppressor genes in combination
with a DNA damaging agent or factor for use in killing cells, and in particular cancerous
cells. A tumor suppressor gene, p53, was delivered via a recombinant adenovirus-mediated
gene transfer both in vitro and in vivo, in combination with a chemotherapeutic agent.
Treated cells underwent apoptosis with specific DNA fragmentation. Direct injection of the
p53-adenovirus construct into tumors subcutaneously, followed by intraperitoneal
administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of
the tumors. The invention also provides for the clinical application of a regimen combining
gene replacement using replication-deficient wild-type p53 adenovirus and DNA-damaging drugs
for treatment of human cancer.

IN: Roth; Jack A., Fujiwara; Toshiyoshi, Grimm; Elizabeth A., Mukhopadhyay; Tapas,
Zhang; Wei-Wei, Owen-Schaub; Laurie B.

14. Document ID: US 6066730 A

L8: Entry 14 of 52

File: USPT

May 23, 2000

US-PAT-NO: 6066730
DOCUMENT-IDENTIFIER: US 6066730 A
TITLE: Boronic ester and acid compounds, synthesis and uses
DATE-ISSUED: May 23, 2000

US-CL-CURRENT: 544/69; 544/229, 546/13, 548/405, 548/953, 558/298, 562/7

APPL-NO: 9/ 085404
DATE FILED: May 26, 1998

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application is a divisional of U.S. application Ser.
No. 08/549,318, filed Oct. 27, 1995, Pat. No. 5,780,454, which is a continuation-in-part of U.S.
application Ser. No. 08/442,581, filed May 16, 1995, pending, which is a continuation-in-part of
U.S. application Ser. No. 08/330,525, filed Oct. 28, 1994, now abandoned, the contents of which
are incorporated herein by reference.

AB: Disclosed herein is a method for reducing the rate of degradation of proteins in
an animal comprising contacting cells of the animal with certain boronic ester and acid
compounds. Also disclosed herein are novel boronic ester and acid compounds, their synthesis
and uses.

IN: Adams; Julian, Ma; Yu-Ting, Stein; Ross, Baevsky; Matthew, Grenier; Louis,
Plamondon; Louis

15. Document ID: US 6060247 A

L8: Entry 15 of 52

File: USPT

May 9, 2000

US-PAT-NO: 6060247
DOCUMENT-IDENTIFIER: US 6060247 A
TITLE: Post-mitotic neurons containing adenovirus vectors that modulate apoptosis and growth
DATE-ISSUED: May 9, 2000

US-CL-CURRENT: 435/6; 435/377, 435/456

APPL-NO: 8/ 995050
DATE FILED: November 18, 1997

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application claims benefit to U.S. Provisional
Application Ser. No. 60/031,057, filed Nov. 18, 1996.

AB: A postmitotic neuron containing an adenovirus vector, the neuron having been
infected with the adenovirus vector at a multiplicity of infection of approximately 10 to
approximately 50, and expressing a gene product encoded by a DNA molecule contained within
said vector.

IN: Miller; Freda D., Slack; Ruth S.

16. Document ID: US 6057104 A

L8: Entry 16 of 52

File: USPT

May 2, 2000

US-PAT-NO: 6057104
DOCUMENT-IDENTIFIER: US 6057104 A
TITLE: Disruption of the mammalian Rad51 protein and disruption of proteins that associate with
mammalian Rad51 for hindering cell proliferation
DATE-ISSUED: May 2, 2000

US-CL-CURRENT: 435/6; 435/196, 530/350, 536/23.2, 536/23.5

APPL-NO: 8/ 964614
DATE FILED: November 5, 1997

PARENT-CASE:
The present application is a continuation-in-part of and claims priority to U.S. applications
Ser. Nos. 08/758,280, filed Nov. 5, 1996. The disclosure of the above application is herein
incorporated by reference.

AB: When a mutation, designated rad51.sup.M1, was generated in the mouse MmRAD51
gene, mutant embryos died shortly after implantation. rad51.sup.M1 cells exhibited
hypersensitivity to ionizing radiation, reduced proliferation, programmed cell death and
chromosome loss. The disruption of MmRad51 protein--protein interactions stopped cell
proliferation and/or reduced cell viability. Several proteins that interact with MmRad51
have been identified including, for example Brca2 and M96. Additionally, Rad51
self-associates via the N-terminal region. When a single residue was changed from a
conserved lysine to an alanine, the alteration proved toxic to cells. Moreover, a rad51
allele that lacked the RecA homology region was also deleterious to cells. In view of the
above, it is clear that inhibiting MmRad51 function or the function of any molecule that
associates with MmRad51, or any molecule in the Rad51 or Rad52 pathways, hinders cell
proliferation and/or viability. Accordingly, molecules capable of blocking these critical
DNA repair pathways may be effective as therapeutics for inhibiting cell proliferation.

IN: Hasty; Paul

17. Document ID: US 6054467 A

L8: Entry 17 of 52

File: USPT

Apr 25, 2000

US-PAT-NO: 6054467
DOCUMENT-IDENTIFIER: US 6054467 A
TITLE: Down-regulation of DNA repair to enhance sensitivity to P53-mediated apoptosis
DATE-ISSUED: April 25, 2000

US-CL-CURRENT: 514/309; 435/7.1, 435/7.23, 514/456, 514/617, 514/619

APPL-NO: 8/ 675887
DATE FILED: July 5, 1996

AB: The present invention details methods for the treatment of cancer. In particular
it concerns the induction of apoptosis in cancer cells following treatment with inhibitors
of DNA repair in combination with p53. Treatment of glioblastoma and breast tumor cells with
inhibitors of DNA repair induced growth suppression that was a result of p53-mediated
apoptosis. Thus it appears that inhibitors of DNA repair in combination with p53 is involved
in restoration of p53-mediated apoptosis.

IN: Gjerset; Ruth A.

18. Document ID: US 6043254 A

L8: Entry 18 of 52

File: USPT

Mar 28, 2000

US-PAT-NO: 6043254
DOCUMENT-IDENTIFIER: US 6043254 A
TITLE: Indolinones having kinase-inhibiting activity
DATE-ISSUED: March 28, 2000

US-CL-CURRENT: 514/310; 514/397, 514/414, 546/143, 548/312.1, 548/465

APPL-NO: 9/ 277063
DATE FILED: March 26, 1999

PARENT-CASE:
RELATED APPLICATIONS The benefit of prior provisional application Ser. No. 60/086,733, filed on
May 26, 1998, is hereby claimed.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
DE	198 15 020	April 3, 1998

AB: The present invention relates to indolinones of general formula ##STR1## wherein
R.sub.1 to R.sub.3 are defined in claim 1, the isomers and the salts thereof, particularly
the physiologically acceptable salts thereof which have valuable pharmacological properties,
particularly an inhibiting effect on various kinases and cycline/CDK complexes and on the
proliferation of various tumour cells, pharmaceutical compositions containing these
compounds, their use and processes for preparing them.

IN: Grell; Wolfgang, Wittneben; Helmut, van Meel; Jacobus Constantinus Antonius,
Redemann; Norbert, Walter; Rainer, Heckel; Armin, Himmelsbach; Frank, Haigh; Robert

19. Document ID: US 6037125 A

L8: Entry 19 of 52

File: USPT

Mar 14, 2000

US-PAT-NO: 6037125
DOCUMENT-IDENTIFIER: US 6037125 A
TITLE: Disruption of the mammalian RAD51 protein and disruption of proteins that associate with
mammalian RAD51 for hindering cell proliferation and/or viability of proliferating cells
DATE-ISSUED: March 14, 2000

US-CL-CURRENT: 435/6

APPL-NO: 8/ 758280
DATE FILED: November 5, 1996

AB: When a mutation, designated rad51.sup.M1, was generated in the mouse MmRAD51
gene, mutant embryos died shortly after implantation. rad51.sup.M1 cells exhibited
hypersensitivity to ionizing radiation, reduced proliferation, programmed cell death and
chromosome loss. The disruption of MmRad51 rotein-protein interactions stopped cell
proliferation and/or reduced cell viability. Several proteins that interact with MmRad51
have been identified including, for example Brca2 and M96. Additionally, Rad51
self-associates via the N-terminal region. When a single residue was changed from a
conserved lysine to an alanine, the alteration proved toxic to cells. Moreover, a rad51
allele that lacked the RecA homology region was also deleterious to cells. In view of the
above, it is clear that inhibiting MmRad51 function or the function of any molecule that
associates with MmRad51, or any molecule in the Rad51 or Rad52 pathways, hinders cell
proliferation and/or viability. Accordingly, molecules capable of blocking these critical
DNA repair pathways may be effective as therapeutics for inhibiting cell proliferation.

IN: Hasty; Paul

20. Document ID: US 6030956 A

L8: Entry 20 of 52

File: USPT

Feb 29, 2000

US-PAT-NO: 6030956
DOCUMENT-IDENTIFIER: US 6030956 A
TITLE: Combination gene therapy for human cancers
DATE-ISSUED: February 29, 2000

US-CL-CURRENT: 514/44; 428/402.2, 435/320.1, 536/23.2, 536/23.5, 536/24.1

APPL-NO: 8/ 956994
DATE FILED: October 23, 1997

PARENT-CASE:
This application claims priority under 37 CFR .sctn.119(e) to Provisional Application Ser. No.
60/029,761 filed Oct. 24, 1996, which is incorporated herein by reference in its entirety.

AB: A method of treating cancer in a subject, by administering to the subject a
combination of genes including wt p53, Pax5 and HSV-tk genes is disclosed. The method may
involve subsequently treating the subject with ganciclovir.

IN: Boulikas; Teni

21. Document ID: US 6025480 A

L8: Entry 21 of 52

File: USPT

Feb 15, 2000

US-PAT-NO: 6025480
DOCUMENT-IDENTIFIER: US 6025480 A
TITLE: Isolated nucleic acid molecules encoding P57KIP2
DATE-ISSUED: February 15, 2000

US-CL-CURRENT: 536/23.1; 435/320.1, 435/325, 435/348, 536/22.1, 536/24.31, 536/24.33

APPL-NO: 8/ 415655
DATE FILED: April 3, 1995

AB: This invention provides an isolated nucleic acid molecule encoding a mammalian
p57.sup.KIP2. This invention also provides vectors comprising the isolated nucleic acid
molecule encoding a mammalian p57.sup.KIP2. This invention further provides a host vector
system for the production of a mammalian p57.sup.KIP2. This invention also provides probes
for the isolated nucleic acid molecule encoding a mammalian p57.sup.KIP2. This invention
provides antibodies directed against a mammalian p57.sup.KIP2. This invention also provides
transgenic animals comprising isolated nucleic acid molecules encoding a mammalian
p57.sup.KIP2. Finally, this invention provides different uses of the mammalian p57.sup.KIP2.

IN: Massague; Joan, Lee; Mong-Hong

22. Document ID: US 6013786 A

L8: Entry 22 of 52

File: USPT

Jan 11, 2000

US-PAT-NO: 6013786
DOCUMENT-IDENTIFIER: US 6013786 A
TITLE: MDM2-specific antisense oligonucleotides
DATE-ISSUED: January 11, 2000

US-CL-CURRENT: 536/24.5; 536/23.1, 536/24.3, 536/24.31

APPL-NO: 9/ 073567
DATE FILED: May 6, 1998

PARENT-CASE:
This is a continuation-in-part of U.S. application Ser. No. 08/916,384, filed Aug. 22, 1997.

AB: The invention provides methods to activate tumor suppressors. The invention
further provides antisense oligonucleotides complementary to a portion of the MDM2-encoding
RNA and methods for using such antisense oligonucleotides as analytical and diagnostic
tools, as potentiators of transgenic animal studies and for gene therapy approaches, and as
potential therapeutic agents. The invention also provides methods to augment and
synergistically activate a tumor suppressor in conjunction with the use of a DNA-damage
inducing agent.

IN: Chen; Jiandong, Agrawal; Sudhir, Zhang; Ruiwen

23. Document ID: US 5997869 A

L8: Entry 23 of 52

File: USPT

Dec 7, 1999

US-PAT-NO: 5997869
DOCUMENT-IDENTIFIER: US 5997869 A
TITLE: Peptides containing a fusion joint of a chimeric protein encoded by DNA spanning a
tumor-associated chromosomal translocation and their use as immunogens
DATE-ISSUED: December 7, 1999

US-CL-CURRENT: 424/184.1; 424/185.1, 424/192.1, 530/300, 530/326, 530/327

APPL-NO: 8/ 528129
DATE FILED: September 14, 1995

PARENT-CASE:
RELATED APPLICATIONS The present application is a Continuation-In-Part of Ser. No. 08/424,573,
filed Apr. 17, 1995, which in turn is a Continuation Application of Ser. No. 08/031,494, filed
Mar. 15, 1993, now abandoned.

AB: A method of immunizing a mammal against a tumor cell by exposing splenic or peripheral blood mononuclear cells to a peptide that encompasses a fusion joint of a fusion protein encoded by DNA spanning a human chromosomal translocation associated with Ewing's sarcoma (t(11;22)(q24;q12)) or alveolar rhabdomyosarcoma (t(2:13)(q35;q14)) is provided.

IN: Goletz; Theresa J., Berzofsky; Jay A., Helman; Lee J.

24. Document ID: US 5990168 A

L8: Entry 24 of 52

File: USPT

Nov 23, 1999

US-PAT-NO: 5990168
DOCUMENT-IDENTIFIER: US 5990168 A
TITLE: Methods and compositions for the treatment of ataxia telangiectasia
DATE-ISSUED: November 23, 1999

US-CL-CURRENT: 514/573; 514/469

APPL-NO: 8/ 844531
DATE FILED: April 17, 1997

PARENT-CASE:
RELATED APPLICATION This Application claims priority to U.S. Provisional Application Serial No. 60/015,810, filed Apr. 18, 1996.

AB: Embodiments of the invention include formulations for the treatment of (AT) ataxia telangiectasia patient and asymptomatic AT heterozygous carriers. The subject formulations comprise one or more different prostaglandins and a pharmaceutically acceptable carrier. Preferably the prostaglandins are group E prostaglandins, prostaglandin E2 being particularly preferred. Other embodiments of the invention include methods of treating AT patients and AT carriers. These methods comprise the steps of administering an effective amount of a prostaglandin containing composition of the invention. Other embodiments of the invention include methods of treating AT patients and carriers with radiotherapy. The methods comprise the steps of administering and effective amount of a prostaglandin containing formulations of the invention and subsequently irradiating the subject with an amount of radiation sufficient to achieve the desired therapeutic effect. Other embodiments of the invention include methods of radioimaging AT patients and AT carriers. The methods comprise the steps of administering an effective amount of a prostaglandin containing formulation of the invention and subsequently irradiating the subject with an amount of radiation to produce a diagnostic image of interest.

IN: Paterson; Malcolm C., Mirzayans; Razmik

25. Document ID: US 5936079 A

L8: Entry 25 of 52

File: USPT

Aug 10, 1999

US-PAT-NO: 5936079
DOCUMENT-IDENTIFIER: US 5936079 A
TITLE: Oligonucleotide which binds to a chromosomal binding site for p53 protein
DATE-ISSUED: August 10, 1999

US-CL-CURRENT: 536/24.5; 435/455

APPL-NO: 8/ 291011
DATE FILED: August 15, 1994

PARENT-CASE:
This is a continuation of application Ser. No. 07/879,618, filed on May 1, 1992, now abandoned, which is a CIP application of U.S. Ser. No. 02/863,661 filed on Apr. 6, 1992, now abandoned.

AB: The present invention provides methods for inhibiting cell growth by providing a growing cell with an oligonucleotide capable of binding to a chromosomal binding site for p53 protein. Moreover, in a preferred embodiment these methods can be used for preventing and treating cancer.

IN: Re; Richard, Cook; Julia

26. Document ID: US 5932210 A

L8: Entry 26 of 52

File: USPT

Aug 3, 1999

US-PAT-NO: 5932210
DOCUMENT-IDENTIFIER: US 5932210 A
TITLE: Recombinant adenoviral vector and methods of use
DATE-ISSUED: August 3, 1999

US-CL-CURRENT: 424/93.2; 424/93.6, 435/320.1

APPL-NO: 8/ 959638
DATE FILED: October 28, 1997

PARENT-CASE:
This application is a continuation of U.S. Ser. No. 08/328,673, filed Oct. 25, 1994, now pending, which is a continuation-in-part of U.S. Ser. No. 08/246,006, filed May 19, 1994, now abandoned, which is a continuation-in-part of U.S. Ser. No. 08/142,669, filed Oct. 25, 1993, now abandoned, the contents of which are hereby incorporated by reference into the present disclosure.

AB: This invention provides a recombinant adenovirus expression vector characterized by the partial or total deletion of the adenoviral protein IX DNA and having a gene encoding a foreign protein or a functional fragment or mutant thereof. Transformed

host cells and a
method of producing recombinant proteins and gene therapy also are included within the scope
of this invention. Thus, for example, the adenoviral vector of this invention can contain a
foreign gene for the expression of a protein effective in regulating the cell cycle, such as
p53, Rb, or mitosin, or in inducing cell death, such as the conditional suicide gene
thymidine kinase. (The latter must be used in conjunction with a thymidine kinase metabolite
in order to be effective).

IN: Gregory; Richard J., Wills; Ken N., Maneval; Daniel C.

27. Document ID: US 5908750 A

L8: Entry 27 of 52

File: USPT

Jun 1, 1999

US-PAT-NO: 5908750
DOCUMENT-IDENTIFIER: US 5908750 A
TITLE: Screening assays for identifying agents that regulate the expression of genes involved in
cell death
DATE-ISSUED: June 1, 1999

US-CL-CURRENT: 435/6; 435/29

APPL-NO: 8/ 838844
DATE FILED: April 11, 1997

PARENT-CASE:
This application is a divisional application of U.S. Ser. No. 08/330,535, filed Oct. 27, 1994,
now U.S. Pat. No. 5,659,024, which is a continuation-in-part of U.S. Ser. No. 08/182,619, filed
Jan. 14, 1994, now U.S. Pat. No. 5,484,710, issued Jan. 14, 1996.

AB: The present invention provides regulatory elements that are linked to genes
involved in cell death. For example, the present invention provides a p53-RE.sup.D, which is
involved in p53-mediated down-regulation of the bcl-2 gene, and the bax promotor, which
contains a p53-RE.sup.U that is involved in p53-mediated up-regulation of the bax gene. The
invention also provides screening assays for identifying agents such as drugs that
effectively modulate expression of a gene that is involved in cell death. In addition, the
invention provides methods for modulating the level of apoptosis in a cell.

IN: Reed; John C., Miyashita; Toshiyuki, Harigai; Masayoshi, Hanada; Motoi

28. Document ID: US 5877210 A

L8: Entry 28 of 52

File: USPT

Mar 2, 1999

US-PAT-NO: 5877210
DOCUMENT-IDENTIFIER: US 5877210 A
TITLE: Phosphotyrosine phosphatase inhibitors or phosphotyrosine kinase activators for
controlling cellular proliferation
DATE-ISSUED: March 2, 1999

US-CL-CURRENT: 514/492; 424/178.1, 424/179.1, 424/181.1, 435/184, 435/244, 556/1, 556/42, 556/44

APPL-NO: 8/ 465813
DATE FILED: June 5, 1995

PARENT-CASE:
CROSS-REFERENCES This application is a continuation-in-part of PCT Application Ser. No.
PCT/US95/01234, filed Jan. 30, 1995 and designating the United States, entitled "Use of
Phosphotyrosine Phosphatase Inhibitors or Phosphotyrosine Kinase Activators for Controlling
Cellular Proliferation," by Gary L. Schieven, which was itself a continuation-in-part of U.S.
application Ser. No. 08/189,330, filed Jan. 31, 1994, now U.S. Pat. No. 5,565,491, also entitled
"Use of Phosphotyrosine Phosphatase Inhibitors or Phosphotyrosine Kinase Activators for
Controlling Cellular Proliferation," by Gary L. Schieven. The disclosures of these two prior
applications are incorporated herein in their entirety by this reference.

AB: A method of inhibiting the proliferation of B cells by using inhibitors of
phosphotyrosine phosphatase can be used to regulate the immune response and to treat
diseases such as leukemias or lymphomas marked by malignant proliferation of B cells or T
cells. Antitumor activity is seen in vivo against tumors and against tumor cell lines. The
use of such inhibitors can be combined with radiation, which produces a synergistic effect.
Several types of inhibitors can be used, including: (1) compounds comprising a metal
coordinate-covalently bound to an organic moiety that can form a five- or six-membered ring,
in which the metal is preferably vanadium (IV); (2) compounds in which vanadium (IV) is
coordinate-covalently bound to an organic moiety such as a hydroxamate, .alpha.-hydroxypyridinone, .alpha.-hydroxypyrone, .alpha.-amino acid, hydroxycarbonyl, or
thiohydroxamate; (3) coordinate-covalent complexes of vanadyl and cysteine or a derivative
thereof; (4) nonhydrolyzable phosphotyrosine phosphatase analogues; (5) dephostatin; (6)
4-(fluoromethyl)phenyl phosphate and esterified derivatives; and (7) coordinate-covalent
metal-organic compounds containing at least one oxo or peroxo ligand bound to the metal, in
which the metal is preferably vanadium (V), molybdenum (VI), or tungsten (VI). Methods of
stimulating signaling in T cells and conjugates of a modulator of phosphotyrosine metabolism
with a specific binding partner for a B cell surface antigen are also disclosed.

IN: Schieven; Gary L.

29. Document ID: US 5866332 A

L8: Entry 29 of 52

File: USPT

Feb 2, 1999

US-PAT-NO: 5866332
DOCUMENT-IDENTIFIER: US 5866332 A
TITLE: Human myeloid terminal differentiation response gene
DATE-ISSUED: February 2, 1999

US-CL-CURRENT: 435/6; 435/252.3, 435/320.1, 435/325, 435/69.1, 435/91.2, 514/44, 536/23.5

APPL-NO: 8/ 602208
DATE FILED: February 15, 1996

PARENT-CASE:
RELATED APPLICATIONS The present invention is a continuation-in-part of then U.S. patent
application Ser. No. 08/221,531, filed Feb. 2, 1994, now abandoned, which is incorporated herein
by reference.

AB: The present invention provides polynucleotide and amino acid sequences which
encode and identify a novel human myeloid terminal differentiation response gene designated
MYD118. The present invention also provides for myd118 antisense molecules. The invention
further provides genetically engineered expression vectors and host cells for the production
of purified MYD118 polypeptide; antibodies, antagonists and inhibitors of MYD118
polypeptide; and pharmaceutical compositions and methods of treatment based on
polynucleotide sequences encoding MYD118 and MYD118 polypeptide. The invention specifically
provides for use of the myd118 polynucleotide sequences as a diagnostic composition for the
detection of myeloproliferative diseases and leukemias. The invention also relates to
therapeutic methods and compositions based upon the nucleotide sequences for myd118. The
invention further provides antibodies which specifically bind to MYD118.

IN: Cocks; Benjamin Graeme, Au-Young; Janice, Seilhamer; Jeffrey J.

30. Document ID: US 5858679 A

L8: Entry 30 of 52

File: USPT

Jan 12, 1999

US-PAT-NO: 5858679
DOCUMENT-IDENTIFIER: US 5858679 A
TITLE: Method for determining the presence of functional p53 by measuring GADD45 protein
expression
DATE-ISSUED: January 12, 1999

US-CL-CURRENT: 435/7.1; 530/386

APPL-NO: 8/ 432176
DATE FILED: May 10, 1995

PARENT-CASE:
The present application is a national filing of PCT International Application No. PCT/US93/11026
filed Nov. 12, 1993, which is a CIP of U.S. Ser. No. 07/974,960 filed Nov. 12, 1992, now
abandoned

PCT-DATA:
APPL-NO
DATE-FILED
PUB-NO
PUB-DATE
371-DATE
102(E)-DATE
PCT/US93/11026
November 12, 1993
WO94/11533
May 26, 1994
May 10, 1995
May 10, 1995

AB: The dependence of ionizing radiation-induced GADD45 mRNA and protein expression
on the presence of functional p53 in mammalian cells is disclosed. First and second
oligonucleotide sequences are provided which can form a double-stranded oligomer capable of
binding to functional p53 protein. The present invention demonstrates that the dependence of
ionizing radiation-induced GADD45 mRNA and protein expression on the presence of functional
p53 and the binding of functional p53 to a double-stranded oligomer binding sequence can
serve as the bases for methods for determining the presence of functional p53 in mammalian
cell lines and tumors.

IN: Fornace, Jr.; Albert J., Kastan; Michael B., Carrier; France

31. Document ID: US 5846998 A

L8: Entry 31 of 52

File: USPT

Dec 8, 1998

US-PAT-NO: 5846998
DOCUMENT-IDENTIFIER: US 5846998 A
TITLE: Use of phosphotyrosine phosphatase inhibitors or phosphotyrosine kinase activators for
controlling cellular proliferation
DATE-ISSUED: December 8, 1998

US-CL-CURRENT: 514/492; 424/617, 424/646, 435/184, 435/326, 556/1, 556/42, 556/44

APPL-NO: 8/ 669499
DATE FILED: June 18, 1996

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATION(S) This is a continuation-in-part of U.S. patent
application Ser. No. 08/189,330, entitled "Use of Phosphotyrosine Phosphatase Inhibitors or
Phosphotyrosine Kinase Activators for Controlling Cellular Proliferation," filed on Jan. 31,
1994, now U.S. Pat. No. 5,565,491, issued Oct. 15, 1996, and is incorporated by reference herein.

PCT-DATA:
APPL-NO

DATE-FILED
PUB-NO
PUB-DATE
371-DATE
102(E)-DATE
PCT/US95/01234
January 30, 1995
WO95/20390
Aug 3, 1995
Jun 18, 1996
Jun 18, 1996

AB: A method of inhibiting the proliferation of B cells by using inhibitors of phosphotyrosine phosphatase can be used to regulate the immune response and to treat diseases such as leukemias or lymphomas marked by malignant proliferation of B cells or T cells. Antitumor activity is seen in vivo against tumors and against tumor cell lines. The use o such inhibitors can be combined with radiation, which produces a synergistic effect. Several types of inhibitors can be used, including: (1) compounds comprising a metal coordinate-covalently bound to an organic moiety that can form a five- or six-membered ring, in which the metal is preferably vanadium (IV); (2) compounds in which vanadium (IV) is coordinate-covalently bound to an organic moiety such as a hydroxamate, .alpha.-hydroxypyridinone, .alpha.-hydroxypyrone, .alpha.-amino acid, hydroxycarbonyl, or thiohydroxamate; (3) coordinate-covalent complexes of cysteine or a derivative thereof; (4) nonhydrolyzable phosphotyrosine analogues; (5) dephostatin; (6) 4-(fluoromethyl)phenyl phosphate and esterified derivatives; and (7) coordinate-covalent metal-organic compounds containing at least one oxo or peroxo ligand bound to the metal, in which the metal is preferably vanadium (V), molybdenum (VI), or tungsten (VI).

IN: Schieven; Gary L.

32. Document ID: US 5847083 A

L8: Entry 32 of 52
File: USPT
Dec 8, 1998

US-PAT-NO: 5847083
DOCUMENT-IDENTIFIER: US 5847083 A
TITLE: Modified p53 constructs which enhance DNA binding
DATE-ISSUED: December 8, 1998

US-CL-CURRENT: 530/358; 435/320.1, 435/69.1, 536/23.4, 536/23.5

APPL-NO: 8/ 697221
DATE FILED: August 21, 1996

AB: A modified p53 protein or peptide having DNA binding in which amino acid residue 284 of a p53 protein or protein fragment is changed to Arginine or Lysine, is described. Also described are nucleotide sequences encoding the modified protein and vectors capable of expressing it.

IN: Halazonetis; Thanos D.

33. Document ID: US 5843773 A

L8: Entry 33 of 52
File: USPT
Dec 1, 1998

US-PAT-NO: 5843773
DOCUMENT-IDENTIFIER: US 5843773 A
TITLE: Apoptosis regulating gene
DATE-ISSUED: December 1, 1998

US-CL-CURRENT: 435/320.1; 435/325, 536/23.1

APPL-NO: 8/ 737980
DATE FILED: November 22, 1996

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY
APPL-NO
APPL-DATE
KR
1995/6266
March 24, 1995

PCT-DATA:
APPL-NO
DATE-FILED
PUB-NO
PUB-DATE
371-DATE
102(E)-DATE
PCT/KR96/00040
March 25, 1996
WO96/30513
Oct 3, 1996
Nov 22, 1996
Nov 22, 1996

AB: A new Bcl-2 related gene "Bfl-1", a polypeptide encoded by said gene, and a plasmid and a transformant comprising said gene are disclosed. The gene can be used to detect cancer.

IN: Shin; Hee Sup, Sung; Young Chul, Hong; Seok Il, Choi; Sun Sim, Yun; Jin Won, Choi; Eun Kyoung, Park; In Chul

34. Document ID: US 5843654 A

L8: Entry 34 of 52
File: USPT
Dec 1, 1998

US-PAT-NO: 5843654
DOCUMENT-IDENTIFIER: US 5843654 A
TITLE: Rapid detection of mutations in the p53 gene

DATE-ISSUED: December 1, 1998

US-CL-CURRENT: 435/6; 435/194, 435/91.1

APPL-NO: 8/ 484956
DATE FILED: June 7, 1995

PARENT-CASE:
This is a Continuation Application of application Ser. No. 08/402,601, filed Mar. 9, 1995, which
is a Continuation-In-Part Application of application Ser. No. 08/337,164, filed Nov. 9, 1994, now
abandoned, which is a Continuation-In-Part Application of application Ser. No. 08/254,359, filed
Jun. 6, 1994, now issued as U.S. Pat. No. 5,614,402 on Mar. 25, 1997, which is a
Continuation-In-Part Application of application Ser. No. 08/073,384, filed Jun. 4, 1993, now
issued as U.S. Pat. No. 5,541,311 on Jul. 30, 1996, which is a Continuation-In-Part Application
of application Ser. No. 07/986,330, filed Dec. 7, 1992, now issued as U.S. Pat. No. 5,422,253 on
Jun. 6, 1995.

AB: The present invention relates to means for cleaving a nucleic acid cleavage
structure in a site-specific manner. Enzymes, including 5' nucleases and 3' exonucleases,
are used to screen for known and unknown mutations, including single base changes, in the
human p53 gene. Methods are provided which allow for the identification of genetic mutations
in the human p53 gene in a sample.

IN: Heisler; Laura M., Fors; Lance, Brow; Mary Ann D.

35. Document ID: US 5831062 A

L8: Entry 35 of 52
File: USPT
Nov 3, 1998

US-PAT-NO: 5831062
DOCUMENT-IDENTIFIER: US 5831062 A
TITLE: Use of the human interferon consensus gene for gene therapy
DATE-ISSUED: November 3, 1998

US-CL-CURRENT: 536/23.52; 536/24.1

APPL-NO: 8/ 852889
DATE FILED: May 8, 1997

AB: The present invention relates generally to a human interferon consensus gene
useful for expression in eucaryotic systems and gene therapy. In particular, the present
invention relates to treatment of cancer and cell proliferation disorders through use of
viral vectors to deliver and express the human interferon consensus gene in the cells and/or
tumors of a patient.

IN: Taylor; Milton W., Blatt; Lawrence M.

36. Document ID: US 5780454 A

L8: Entry 36 of 52
File: USPT
Jul 14, 1998

US-PAT-NO: 5780454
DOCUMENT-IDENTIFIER: US 5780454 A
TITLE: Boronic ester and acid compounds
DATE-ISSUED: July 14, 1998

US-CL-CURRENT: 514/64; 544/229

APPL-NO: 8/ 549318
DATE FILED: October 27, 1995

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application is a continuation-in-part of U.S.
application Ser. No. 08/442,581, filed May 16, 1995, which is a continuation-in-part of U.S.
application No. 08/330,525, filed Oct. 28, 1994, now abandoned, the contents of which are
incorporated herein by reference.

AB: Disclosed herein is a method for reducing the rate of degradation of proteins in
an animal comprising contacting cells of the animal with certain boronic ester and acid
compounds. Also disclosed herein are novel boronic ester and acid compounds, their synthesis
and uses.

IN: Adams; Julian, Ma; Yu-Ting, Stein; Ross, Baevsky; Matthew, Grenier; Louis,
Plamondon; Louis

37. Document ID: US 5776743 A

L8: Entry 37 of 52
File: USPT
Jul 7, 1998

US-PAT-NO: 5776743
DOCUMENT-IDENTIFIER: US 5776743 A
TITLE: Method of sensitizing tumor cells with adenovirus E1A
DATE-ISSUED: July 7, 1998

US-CL-CURRENT: 435/6; 424/93.1, 424/93.2, 424/93.21, 435/235.1, 435/325, 435/363, 435/366,
435/367, 435/368, 435/369, 435/370, 435/371, 514/44, 536/23.72, 536/72

APPL-NO: 8/ 301316
DATE FILED: September 6, 1994

AB: The present invention is directed to methods of sensitizing a human tumor cell
with adenovirus E1A. The methods involve treating a human tumor cell by, first, introducing
into the tumor cell nucleic acid encoding a polypeptide having adenovirus E1A activity,
expressing the E1A active polypeptide in the cell, and then either contacting the E1A
expressing tumor cell with a chemotherapeutic agent or irradiating the E1A-expressing tumor
cell. The invention also provides methods of enhancing a subject's

response to chemotherapy
or irradiation by introducing into a subject's tumor cells nucleic acid encoding a
polypeptide having adenovirus E1A activity, expressing the E1A active polypeptide in the
cells and finally, administering either a chemotherapeutic agent or irradiation. The
invention also provides a method of treating cancer.

IN: Frisch; Steven M.

38. Document ID: US 5770377 A

L8: Entry 38 of 52

File: USPT

Jun 23, 1998

US-PAT-NO: 5770377
DOCUMENT-IDENTIFIER: US 5770377 A
TITLE: Interruption of binding of MDM2 and P53 protein and therapeutic application thereof
DATE-ISSUED: June 23, 1998

US-CL-CURRENT: 435/7.1; 435/7.23, 435/7.9, 435/7.91, 435/7.92, 435/7.93, 436/501, 436/518,
436/523, 436/524, 436/525, 436/526, 436/527, 436/528, 436/529, 436/530, 436/531, 436/64, 436/813

APPL-NO: 8/ 424957
DATE FILED: April 19, 1995

PARENT-CASE:
This application is a continuation-in-part application of U.S. Ser. No. 08/277,660, filed Jul.
20, 1994, pending.

AB: A method for interfering with the binding between p53 and MDM2 or a protein
having a p53 binding site analogous to that of MDM2, which method comprises administering a
effective amount of a compound, selected from the group consisting of a peptide having up to
twenty eight amino acids which is able to disrupt or prevent binding between p53 and MDM2,
or a functional peptide analogue thereof., Compounds for use in the method, methods for
detecting such compounds and their application in the diagnosis and treatment of tumours is
also described and claimed.

IN: Picksley; Steven Michael, Lane; David Philip

39. Document ID: US 5747650 A

L8: Entry 39 of 52

File: USPT

May 5, 1998

US-PAT-NO: 5747650
DOCUMENT-IDENTIFIER: US 5747650 A
TITLE: P53AS protein and antibody therefor
DATE-ISSUED: May 5, 1998

US-CL-CURRENT: 530/387.7; 530/387.1, 530/388.8, 530/389.1, 530/389.2

APPL-NO: 8/ 644456
DATE FILED: May 10, 1996

PARENT-CASE:
This is a continuation-in-part of U.S. patent application Ser. No. 08/106,496, filed Aug. 2,
1993.

AB: In accordance with the present invention, we have discovered and purified a
protein designated herein as p53as, which protein is present in normal cells of a mammal and
is essentially identical to known normal growth controlling protein p53 of the same mammal,
at least until the final 50 amino acids of the carboxy terminal end of the protein. The
invention further includes an antibody specific for protein p53as, which antibody is
designated herein as Ab p53as. The antibody may be either a monoclonal or polyclonal
antibody and may be specific for p53as of any particular mammal such as mice and humans.

IN: Kulesz-Martin; Molly F.

40. Document ID: US 5747469 A

L8: Entry 40 of 52

File: USPT

May 5, 1998

US-PAT-NO: 5747469
DOCUMENT-IDENTIFIER: US 5747469 A
TITLE: Methods and compositions comprising DNA damaging agents and p53
DATE-ISSUED: May 5, 1998

US-CL-CURRENT: 514/44; 435/320.1, 435/375, 514/2

APPL-NO: 8/ 233002
DATE FILED: April 25, 1994

PARENT-CASE:
The present application is a continuation-in-part of co-pending U.S. patent application Ser. No.
08/145,826, filed Oct. 29, 1993; which is a continuation-in-part of U.S. patent application Ser.
No. 07/960,513, filed Oct. 13, 1992; which is a continuation-in-part of U.S. Ser. No. 07/665,538,
filed Mar. 6, 1991 now abandoned; the entire text and figures of which disclosures are
incorporated herein by reference without disclaimer.

AB: The present invention relates to the use of tumor suppressor genes in combination
with a DNA damaging agent or factor for use in killing cells, and in particular cancerous
cells. A tumor suppressor gene, p53, was delivered via a recombinant adenovirus-mediated
gene transfer both in vitro and in vivo, in combination with a chemotherapeutic agent.
Treated cells underwent apoptosis with specific DNA fragmentation. Direct injection of the

p53-adenovirus construct into tumors subcutaneously, followed by intraperitoneal
administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of
the tumors. The invention also provides for the clinical application of a regimen combining
gene replacement using replication-deficient wild-type p53 adenovirus and DNA-damaging drugs
for treatment of human cancer.

IN: Roth; Jack A., Fujiwara; Toshiyoshi, Grimm; Elizabeth A., Mukhopadhyay; Tapas,
Zhang; Wei-Wei, Owen-Schaub; Laurie B.

41. Document ID: US 5744310 A

L8: Entry 41 of 52

File: USPT

Apr 28, 1998

US-PAT-NO: 5744310
DOCUMENT-IDENTIFIER: US 5744310 A
TITLE: Bax promoter sequence and screening assays for indentifying agents that regulate bax gene
expression
DATE-ISSUED: April 28, 1998

US-CL-CURRENT: 435/6; 435/325, 435/69.1, 435/91.4, 536/24.1

APPL-NO: 8/ 688145
DATE FILED: July 29, 1996

AB: The present invention provides a substantially purified bax promoter and a
nucleic acid molecule containing a nucleotide sequence encoding a gene product operably
linked to a bax promoter. The invention also provides a substantially purified active
fragment of a bax promoter and a nucleic acid molecule containing a nucleotide sequence
encoding a gene product operably linked to an active fragment of a bax promoter. Cell-based
screening assays for identifying an effective agent such as a drug that regulates the level
of expression of a gene operably linked to a bax promoter, or an active fragment thereof,
also are provided.

IN: Reed; John C.

42. Document ID: US 5721340 A

L8: Entry 42 of 52

File: USPT

Feb 24, 1998

US-PAT-NO: 5721340
DOCUMENT-IDENTIFIER: US 5721340 A
TITLE: p53 proteins with altered tetramerization domains
DATE-ISSUED: February 24, 1998

US-CL-CURRENT: 530/350; 435/320.1, 435/69.7, 435/7.1, 530/352, 530/358, 536/23.1

APPL-NO: 8/ 431357
DATE FILED: April 28, 1995

PARENT-CASE:
I. CROSSED-REFERENCE WITH OTHER APPLICATIONS This is a continuation-in-part of U.S. patent
application Ser. No. 08/347,792, filed Nov. 28, 1994, now U.S. Pat. No. 5,573,925.

AB: The present invention provides p53 proteins with altered tetramerization domains
that retain wild-type p53 function, and the ability to form tetramers and have at least one
of the following characteristics: (1) do not hetero-oligomerize with wild-type p53 or
tumor-derived p53 mutants, and (2) restricted DNA binding specificity from an alteration in
the way that the tetramerization domain orients the DNA binding domains of a p53 tetramer
relative to one another. The invention also provides nucleic acids encoding the above
proteins and methods of enhancing the cellular response to DNA damaging agents, treating
diseases characterized by abnormal cell proliferation, and inducing immune tolerance to
facilitate transplants and treatment of autoimmune disease, by administration of proteins of
the invention or nucleic acid sequences encoding the proteins of the invention.

IN: Halazonetis; Thanos D.

43. Document ID: US 5702908 A

L8: Entry 43 of 52

File: USPT

Dec 30, 1997

US-PAT-NO: 5702908
DOCUMENT-IDENTIFIER: US 5702908 A
TITLE: Interruption of binding of MDM2 and p53 protein and therapeutic application thereof
DATE-ISSUED: December 30, 1997

US-CL-CURRENT: 435/7.8

APPL-NO: 8/ 277660
DATE FILED: July 20, 1994

AB: A method of identifying a compound which interferes with the binding of MDM2 to
human p53 has been determined. This method comprises forming a mixture between MDM2 and a
fragment of human p53 consisting of 6 to 28 amino acids comprising TFSDLW (SEQ ID NO:2),
adding a test compound to the mixture and determining the quantity of protein bound to the
other before and after adding the compound. A compound which decreases the amount of binding
of the two proteins to each other is a compound which interferes with the binding of MDM2 to
human p53.

IN: Picksley; Steven Michael, Lane; David Philip

44. Document ID: US 5693617 A

L8: Entry 44 of 52

File: USPT

Dec 2, 1997

US-PAT-NO: 5693617
DOCUMENT-IDENTIFIER: US 5693617 A
TITLE: Inhibitors of the 26s proteolytic complex and the 20s proteasome contained therein
DATE-ISSUED: December 2, 1997

US-CL-CURRENT: 514/18; 514/19, 530/331, 560/159, 560/20, 560/27, 560/31, 560/32, 560/41, 560/47

APPL-NO: 8/ 404866
DATE FILED: January 15, 1995

PARENT-CASE:
CROSS-REFERENCES TO RELATED APPLICATIONS This application is a continuation-in-part of U.S.
patent application Ser. No. 08/212,909 filed Mar. 15, 1994, abandoned. The disclosure of this
earlier filed application is hereby incorporated herein by reference.

AB: Disclosed herein is a method for reducing the rate of degradation of proteins in
an animal comprising contacting cells of the animal with certain proteasome inhibitors. The
structure of the inhibitors are also disclosed.

IN: Stein; Ross L., Ma; Yu-Ting, Brand; Stephen

45. Document ID: US 5659024 A

L8: Entry 45 of 52

File: USPT

Aug 19, 1997

US-PAT-NO: 5659024
DOCUMENT-IDENTIFIER: US 5659024 A
TITLE: Promotors that regulate the expression of genes involved in cell death
DATE-ISSUED: August 19, 1997

US-CL-CURRENT: 536/24.1; 536/23.1

APPL-NO: 8/ 330535
DATE FILED: October 27, 1994

PARENT-CASE:
This application is a continuation-in-part of United States Ser. No. 08/182,619, filed Jan. 14
1994, now U.S. Pat. No. 5,484,710.

AB: The present invention provides regulatory elements that are linked to genes
involved in cell death. For example, the present invention provides a p53-RE.sup.D, which is
involved in p53-mediated down-regulation of the bcl-2 gene, and the bax promotor, which
contains a p53-RE.sup.U that is involved in p53-mediated up-regulation of the bax gene. The
invention also provides screening assays for identifying agents such as drugs that
effectively modulate expression of a gene that is involved in cell death. In addition, the
invention provides methods for modulating the level of apoptosis in a cell.

IN: Reed; John C., Miyashita; Toshiyuki, Harigai; Masayoshi, Hanada; Motoi

46. Document ID: US 5643727 A

L8: Entry 46 of 52

File: USPT

Jul 1, 1997

US-PAT-NO: 5643727
DOCUMENT-IDENTIFIER: US 5643727 A
TITLE: BCL-2 gene inhibitory element binding factor
DATE-ISSUED: July 1, 1997

US-CL-CURRENT: 435/6; 530/350, 530/358, 536/24.1

APPL-NO: 8/ 390858
DATE FILED: February 16, 1995

AB: The present invention provides a bcl-2 gene inhibitory element (BIE), which can
inhibit expression of a gene in position-dependent and orientation-dependent manner. The
invention provides, for example, BIE-1, having the nucleotide sequence 5'-CAAGAATGCAA-3'
(SEQ ID NO: 1), which acts in an orientation-dependent and position-dependent manner to
down-regulate the expression of the bcl-2 gene. The invention also provides a BIE binding
factor (BBF), which is a cellular factor that can bind to a BIE. The invention provides, for
example, BBF-A, which binds to BIE-1, including a nucleic acid sequence (SEQ ID NO: 8)
encoding a portion of the amino acid sequence (SEQ ID NO: 9) of BBF-A. The invention further
provides an antibody that specifically binds BBF-A. The invention also provides screening
assays for identifying agents that can increase or decrease the binding of a BBF to a BIE,
modulate the expression of a nucleic acid molecule linked to a BIE or modulate apoptosis in
a cell.

IN: Reed; John C., Harigai; Masayoshi

47. Document ID: US 5616463 A

L8: Entry 47 of 52

File: USPT

Apr 1, 1997

US-PAT-NO: 5616463
DOCUMENT-IDENTIFIER: US 5616463 A

TITLE: Methods for determining the presence of functional p53 in mammalian cells
DATE-ISSUED: April 1, 1997

US-CL-CURRENT: 435/6; 536/23.5

APPL-NO: 8/ 288872
DATE FILED: August 10, 1994

PARENT-CASE:
This is a continuation of application Ser. No. 07/974,960, filed on Nov. 12, 1992 now abandoned.

AB: The dependence of ionizing radiation-induced GADD45 mRNA expression on the presence of functional p53 in mammalian cells is disclosed. First and second oligonucleotide sequences are provided which can form a double-stranded oligomer capable of binding to functional p53 protein. The present invention demonstrates that the dependence of ionizing radiation-induced GADD45 mRNA expression on the presence of functional p53 and the binding of functional p53 to a double-stranded oligomer binding sequence can serve as the basis for methods for determining the presence of functional p53 in mammalian cell lines and tumors.

IN: Fornace, Jr.; Albert J., Kastan; Michael B.

48. Document ID: US 5573925 A

L8: Entry 48 of 52

File: USPT

Nov 12, 1996

US-PAT-NO: 5573925
DOCUMENT-IDENTIFIER: US 5573925 A
TITLE: P53 proteins with altered tetramerization domains
DATE-ISSUED: November 12, 1996

US-CL-CURRENT: 435/69.7; 514/44, 530/350, 536/23.4

APPL-NO: 8/ 347792
DATE FILED: November 28, 1994

AB: The present invention provides p53 proteins with altered tetramerization domains that retain wild-type p53 function, and the ability to form tetramers and have at least one of the following characteristics: (1) do not hetero-oligomerize with wild-type p53 or tumor-derived p53 mutants, and (2) restricted DNA binding specificity from an alteration in the way that the tetramerization domain orients the DNA binding domains of a p53 tetramer relative to one another. The invention also provides nucleic acids encoding the above proteins and methods of enhancing the cellular response to DNA damaging agents, treating diseases characterized by abnormal cell proliferation, and inducing immune tolerance to facilitate transplants and treatment of autoimmune disease, by administration of proteins of the invention or nucleic acid sequences encoding the proteins of the invention.

IN: Halazonetis; Thanos D.

08/918407
A44430

=> s p53
L1 89463 P53

=> s dna(3n)damag?
L2 94521 DNA(3N) DAMAG?

=> s l1 and l2
L3 9199 L1 AND L2

=> s tumor(w)suppress?
L4 64218 TUMOR(W) SUPPRESS?

=> s l1 and l2 and l3
L5 9199 L1 AND L2 AND L3

=> s l5 and py<1994
1 FILES SEARCHED...
3 FILES SEARCHED...
4 FILES SEARCHED...
L6 233 L5 AND PY<1994

=> s l6(l)l1
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH FIELD CODE - 'AND' OPERATOR ASSUMED 'L31(L)L1'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH FIELD CODE - 'AND' OPERATOR ASSUMED 'L32(L)L2'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH FIELD CODE - 'AND' OPERATOR ASSUMED 'L33(L)L3'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH FIELD CODE - 'AND' OPERATOR ASSUMED 'L34(L)L4'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH FIELD CODE - 'AND' OPERATOR ASSUMED 'L35(L)L5'
L7 233 L6(L) L1

=> dup rem l6
PROCESSING COMPLETED FOR L6
L8 126 DUP REM L6 (107 DUPLICATES REMOVED)

=> s tumor?
L9 1964692 TUMOR?

=> s l8 and l9
L10 82 L8 AND L9

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11 82 DUP REM L10 (0 DUPLICATES REMOVED)

=> d l11 ibib abs 1-82

L11 ANSWER 1 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94016118 EMBASE
DOCUMENT NUMBER: 1994016118
TITLE: The mdm-2 gene is induced in response to UV light in a ***p53*** -dependent manner.
AUTHOR: Perry M.E.; Piette J.; Zawadzki J.A.; Harvey D.; Levine A.J.
CORPORATE SOURCE: Department of Molecular Biology, Princeton University,Princeton, NJ 08544-1014, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1993) 90/24 (11623-11627). ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Irradiation of mammalian cells with UV light results in a dose-dependent
accumulation of the ***p53*** ***tumor*** -suppressor gene product
that is evident within 2 hr. UV treatment causes a dramatic increase in ***p53*** -specific transcriptional transactivation activity and an increase in expression of the ***p53*** -responsive gene mdm-2. UV-stimulated mdm-2 expression is not directly correlated with the level of ***p53*** protein in a cell because mdm-2 induction is delayed at high UV doses even though ***p53*** levels rise almost immediately. Cells lacking ***p53*** protein do not respond to UV by increasing their expression of mdm-2. The delayed induction of mdm-2 at high UV doses
suggests that, in addition to ***p53*** protein levels, other factors contribute to the regulation of mdm-2 expression following UV treatment. The time of induction of mdm-2 in cells treated with UV light correlates with recovery of normal rates of DNA synthesis, presumably after DNA repair. These data indicate a possible role for mdm-2 in cell cycle progression.

L11 ANSWER 2 OF 82 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:100688 HCAPLUS
DOCUMENT NUMBER: 120:100688
TITLE: Induction of cellular ***p53*** activity by ***DNA*** - ***damaging*** agents and growth arrest. [Erratum to document cited in CA119(19):198646g]
AUTHOR(S): Zhan, Qimin; Carrier, France; Fornace, Albert, J., Jr.
CORPORATE SOURCE: Lab. Mol. Pharmacol., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Mol. Cell. Biol. (***1993***), 13(9), 5928 CODEN: MCEBD4; ISSN: 0270-7306
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The errors were not reflected in the abstr. or the index entries.

L11 ANSWER 3 OF 82 MEDLINE
ACCESSION NUMBER: 94061852 MEDLINE
DOCUMENT NUMBER: 94061852 PubMed ID: 8242631
TITLE: TP53 gene mutation profile in esophageal squamous cell carcinomas.
AUTHOR: Audrezet M P; Robaszkiewicz M; Mercier B; Nousbaum J B; Bail J P; Hardy E; Volant A; Lozac'h P; Charles J F; Goueron H; +
CORPORATE SOURCE: Centre de Biogenetique, C.D.T.S., Brest, France.
SOURCE: CANCER RESEARCH, ***(1993 Dec 1)*** 53 (23) 5745-9.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940201
Last Updated on STN: 19940201
Entered Medline: 19940103
AB Esophageal squamous cell carcinoma is a form of cancer occurring most commonly in males, particularly those living in some areas of Asia, Africa, and western Europe. In some of these ***tumors*** , a sequence alteration has been identified in the coding region of the TP53 gene which is known to inactivate the ***tumor*** suppressor function of its product. Using a GC clamp (i.e., a GC rich domain) denaturing gradient gel
electrophoresis assay we have been able to identify sequence modifications
in 27 of the 32 ***tumor*** samples analyzed (84%). Most of the mutations occur in exon 6, a region of the gene which has not previously been reported as being a hot spot for the mutations of other cancers. Twelve of the mutations reported here have not been described in other types of ***tumors*** and these consist mostly of frameshift or splice mutations. The distribution of mutations [transitions (45%), transversions (34%), and frameshift (21%)] suggests that the etiological contribution of genotoxic factors might be complex and might associate different exogenous
and endogenous mutagen exposures.

L11 ANSWER 4 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:367781 BIOSIS
DOCUMENT NUMBER: PREV199396053456
TITLE: ***P53*** mutations increase resistance to ionizing radiation.
AUTHOR(S): Lee, Jonathan M.; Bernstein, Alan (1)
CORPORATE SOURCE: (1) Div. Molecular Developmental Biol., Samuel Lunenfeld
Res. Inst., Mount Sinai Hosp., 600 University Avenue,

Toronto, ON, Canada M5G 1X5
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1993) Vol. 90, No. 12, pp. 5742-5746.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Mouse and human ***tumors*** of diverse origin frequently have somatically acquired mutations or rearrangements of the ***p53*** gene, or they have lost one or both copies of the gene. Although wild-type ***p53*** protein is believed to function as a ***tumor*** -suppressor gene, it is as yet unclear how ***p53*** mutations lead to neoplastic development. Wild-type ***p53*** has been postulated to play a role in DNA repair, suggesting that expression of mutant forms of ***p53*** might alter cellular resistance to the ***DNA*** ***damage*** caused by gamma radiation. Moreover, ***p53*** is thought to function as a cell cycle checkpoint after irradiation, also suggesting that mutant ***p53*** might change the cellular proliferative response to radiation. We have used transgenic mice expressing one of two mutant alleles of ***p53*** to test this prediction. Our results show that expression of both mutant variants of the mouse ***p53*** gene significantly increases the cellular resistance of a variety of hematopoietic cell lineages to gamma radiation. These observations provide direct evidence that ***p53*** mutations affect the cellular response to ***DNA*** ***damage*** , either by increasing ***DNA*** repair processes or, possibly, by increasing cellular tolerance to ***DNA*** ***damage*** . The association of ***p53*** mutations with increased radioresistance suggests possible mechanisms through which alterations in the ***p53*** gene might lead
to oncogenic transformation.

L11 ANSWER 5 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:34916 BIOSIS
DOCUMENT NUMBER: PREV199497047916
TITLE: DNA strand bias in the repair of the ***p53*** gene in normal human and xeroderma pigmentosum group C fibroblasts.
AUTHOR(S): Evans, Michele K. (1); Taffe, Bonita G. (1); Harris, Curtis
C.; Bohr, Vilhelm A. (1)
CORPORATE SOURCE: (1) Lab. Mol. Genetics, Natl. Inst. Aging, NIH, Baltimore,
MD 21224 USA
SOURCE: Cancer Research, (1993) Vol. 53, No. 22, pp. 5377-5381.
ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We have measured the gene-specific and strand-specific DNA repair of UV-induced cyclobutane pyrimidine dimers in the ***p53*** ***tumor*** suppressor gene in a normal, repair-proficient human fibroblast strain and in fibroblasts from a patient with the repair deficient disorder xeroderma pigmentosum, complementation xeroderma pigmentosum group C (XP-C). In both cell strains, repair was measured in the ***p53*** gene and in its individual DNA strands. For comparison, the repair also was measured in other genomic regions in these human fibroblast strains, including the housekeeping gene dihydrofolate reductase, and two inactive genomic regions, the delta globin gene, and the 754 locus of the X chromosome. In both cell strains, we find that the ***p53*** gene is repaired faster than the dihydrofolate reductase gene and much more efficiently than the inactive genomic regions. Selective repair of the transcribed DNA strand of ***p53*** is observed in both human cell strains; the strand bias of repair is particularly distinct in XP-C. Mutations specific to the nontranscribed strand may occur due to replication errors at the sites of unrepaired ***DNA*** ***damage***

. Therefore, our results predict that the majority of mutations in skin cancers, especially those from patients with XP-C, would occur on the nontranscribed strand of the ***p53*** gene. Indeed, Dumasz et al. (Proc. Natl. Acad. Sci. USA, in press, 1993) report such a strand bias of ***p53*** mutation in skin cancers from XP-C patients.

L11 ANSWER 6 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:588386 BIOSIS
DOCUMENT NUMBER: PREV199497007756
TITLE: Role of the ***p53*** ***tumor*** -suppressor gene in cell cycle arrest and radiosensitivity of Burkitt's lymphoma cell lines.
AUTHOR(S): O'Connor, Patrick M. (1); Jackman, Joany; Jondle, Daniel;
Bhatia, Kishor; Magrath, Ian; Kohn, Kurt W.
CORPORATE SOURCE: (1) Room 5C-25, Bldg. 37, National Cancer Inst., Bethesda,
MD 20892 USA
SOURCE: Cancer Research, (1993) Vol. 53, No. 20, pp. 4776-4780.
ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We have assessed the role of the ***p53*** ***tumor*** suppressor
gene in cell cycle arrest and cytotoxicity of ionizing radiation in 17 Burkitt's lymphoma and lymphoblastoid cell lines. Cell cycle arrest was assessed by flow cytometry of cells 16 h following irradiation. In addition to the usual G-2 arrest, the cell lines exhibited three types of responses in G-1: Class I, strong arrest in G-1 following radiation; Class II, minimal arrest; and Class III, an intermediate response. All Class I cells contained normal ***p53*** genes. Of the ten lines that showed minimal G-1 arrest, eight bad mutant ***p53*** alleles, and two lines were heterozygous for ***p53*** mutations. Both of the lines showing an intermediate response contained wild-type ***p53*** . Our results are consistent with the view that mutations abrogate the ability of ***p53*** to induce G-1 arrest following radiation. Studies with the heterozygotes showed that the mutant protein can have a dominant negative
influence upon wild-type ***p53*** , and the reduced ability of two normal ***p53*** lines to arrest in G-1 indicated that ***p53*** function can be impaired by other mechanisms. The radiosensitivity of most
of the lines appeared to depend on the ability of ***p53*** to induce a G-1 arrest. The mean radiation dose that inhibited proliferation of the Class I lines by 50% was 0.98 Gy. Of the eight ***p53*** mutant cell lines tested, five lines required approximately 2.9 Gy to cause a 50% inhibition of cell proliferation. The two heterozygotes were also more resistant to radiation than the Class I cells (50% inhibitory dose, 2.1 and 2.9 Gy). Our results suggest that radioresistance is afforded by a loss of function of wild-type ***p53*** , which would normally induce a
G-1 arrest and promote cell death in the presence of ***DNA*** ***damage*** .

L11 ANSWER 7 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:365729 BIOSIS
DOCUMENT NUMBER: PREV199396051404
TITLE: Induction of cellular ***p53*** activity by ***DNA*** - ***damaging*** agents and growth arrest.
AUTHOR(S): Zhan, Qimin; Carrier, France; Fornace, Albert J., Jr. (1)
CORPORATE SOURCE: (1) Lab. Mol. Pharmacol., DTP, DCT, Natl. Cancer Inst.,
Room 5C09, Build. 37, Bethesda, MD 20892 USA
SOURCE: Molecular and Cellular Biology, (1993) Vol. 13, No. 7, pp.
4242-4250.
ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The ***tumor*** suppressor ***p53*** can function as a sequence-specific transcription factor and is required for activation by ionizing radiation (IR) of one or more downstream effector genes, such as the human GADD45 gene. One important consequence of IR that is probably
mediated by these downstream effector genes is activation of the ***p53*** -mediated G-1 cell cycle checkpoint. While the induction of reporter constructs containing ***p53*** -binding sites has already been demonstrated with ***p53*** expression vectors, we have now demonstrated the direct activation of such a construct after treatment of the human RKO line, which has a normal ***p53*** phenotype, with various types of ***DNA*** - ***damaging*** agents and also after growth arrest produced by medium depletion (starvation). IR, UV radiation,
and methylmethane sulfonate were found to induce ***p53*** activity when a stably integrated reporter construct containing functional ***p53*** -binding sites was used and also in mobility shift assays with a ***p53*** -binding site from the GADD45 gene, and IR-inducible gene
previously associated with growth arrest. The same cell treatments that induced this ***p53*** activity also caused an increase in cellular ***p53*** protein levels. The response in cells lacking normal

p53 or in RKO cells expressing a dominant negative mutant ***p53*** was markedly reduced. Interestingly, the spectrum of effective inducing agents for the above-described experiments was similar to that which induces GADD45 either in cells with a normal ***p53*** status or, with the exception of IR, in cells lacking normal ***p53*** . These results indicate a role for pS3 in the IR pathway, which is completely ***p53*** dependent, and in other genotoxic stress responses, in which ***p53*** has a cooperative effect but is not required.

L11 ANSWER 8 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:321952 BIOSIS
DOCUMENT NUMBER: PREV199396030302
TITLE: Human papillomavirus 16 E6 expression disrupts the ***p53*** -mediated cellular response to ***DNA*** ***damage*** .
AUTHOR(S): Kessis, Theodore D.; Slebos, Robbert J.; Nelson, William G.; Kastan, Michael B.; Plunkett, Beverly S.; Han, Sung M.; Lorincz, Attila T.; Hedrick, Lora (1); Cho, Kathleen R. (1)
CORPORATE SOURCE: (1) Dep. Pathol., Johns Hopkins Univ. Sch. Med., Baltimore, MD 21205 USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1993) Vol. 90, No. 9, pp. 3988-3992.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Infection with certain types of human papillomaviruses (HPV) is highly associated with carcinomas of the human uterine cervix. However, HPV infection alone does not appear to be sufficient for the process of malignant transformation, suggesting the requirement of additional cellular events. After ***DNA*** ***damage*** , normal mammalian cells exhibit G-1 cell-cycle arrest and inhibition of replicative DNA synthesis. This mechanism, which requires wild-type ***p53*** , presumably allows cells to undertake DNA repair and avoid the fixation of mutations. We directly tested whether the normal response of cervical epithelial cells to ***DNA*** ***damage*** may be undermined by interactions between the E6 protein expressed by oncogenic HPV types and wild-type ***p53*** . We treated primary keratinocytes with the ***DNA*** - ***damaging*** agent actinomycin D and demonstrated inhibition of replicative DNA synthesis and a significant increase in ***p53*** protein levels. In contrast, inhibition of DNA synthesis and increases in ***p53*** protein did not occur after actinomycin D treatment of keratinocytes immortalized with HPV16 E6/E7 or in cervical carcinoma cell lines containing HPV16, HPV18, or mutant ***p53*** alone. To test the effects of E6 alone on the cellular response to ***DNA*** ***damage*** , HPV16 E6 was expressed in the carcinoma cell line RKO, resulting in undetectable baseline levels of ***p53*** protein and loss of the G, arrest that normally occurs in these cells after ***DNA*** ***damage*** . These findings demonstrate that oncogenic E6 can disrupt an important cellular response to ***DNA*** ***damage*** mediated by ***p53*** and may contribute to the subsequent accumulation of genetic changes associated with cervical ***tumorigenesis*** .

L11 ANSWER 9 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:457087 BIOSIS
DOCUMENT NUMBER: PREV199396101987
TITLE: ***P53*** Mutation does not correlate with radiosensitivity in 24 head and neck cancer cell lines.
AUTHOR(S): Brachman, David G. (1); Beckett, Michael; Graves, Deborah; Haraf, Daniel; Vokes, Everett; Weichselbaum, Ralph R.
CORPORATE SOURCE: (1) Dep. Radiation Cellular Oncol., Univ. Chicago Hosp., Chicago, IL 60637
SOURCE: Cancer Research, (1993) Vol. 53, No. 16, pp. 3667-3669.
ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The molecular basis of ***tumor*** response to therapeutic radiation is poorly understood. Recent evidence suggests the ***p53*** ***tumor*** suppressor gene may be involved in production of the G-1 arrest seen following ***DNA*** ***damage*** by X-irradiation. It has further been proposed that ***tumor*** cells lacking the ***p53*** checkpoint function are likely to be more sensitive to cell killing by X-irradiation because these cells enter S phase despite unrepaired ***DNA*** ***damage*** . We tested the hypothesis that ***tumor*** cells with ***p53*** mutations are more radiosensitive by correlating the in vitro surviving fraction at 2 Gy with the mutational status of 24 head and neck squamous cell cancer cell lines. ***p53*** mutations were present in 15 of 24 (63%) of ***tumors*** ; all were homozygous changes occurring within exons 5-9. The surviving fraction at 2 Gy for the group with mutations was 0.568 compared to 0.507 for ***tumors*** without mutations (P = 0.28, Mann-Whitney test). Furthermore, no association between radiosensitivity and mutational type, codon location, or predicted amino acid alteration was noted. Our data do not support the hypothesis that ***p53*** gene alteration predisposes ***tumor*** cells to increased cell killing via radiation.

L11 ANSWER 10 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93229634 EMBASE
DOCUMENT NUMBER: 1993229634
TITLE: Accumulation of wild type ***p53*** protein in human astrocytomas.
AUTHOR: Rubio M.-P.; Von Deimling A.; Yandell D.W.; Wiestler O.D.; Gusella J.F.; Louis D.N.
CORPORATE SOURCE: Molecular Neuro-Oncology Laboratory, Massachusetts General Hospital,Charlestown, MA 02129, United States
SOURCE: Cancer Research, (1993) 53/15 (3465-3467).
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have previously described 10 astrocytomas with accumulation of ***p53*** protein but no mutations in ***p53*** exons 5-8, and we have suggested that they might represent overexpression of wild type protein or mutations in less conserved regions of the gene. To investigate these possibilities further, we studied the ***tumors*** with immunohistochemistry for wild type and mutant ***p53*** protein and showed that all cases stained with the wild type PAb 1801 antibody but only one case stained with the mutant-specific PAb 240 antibody. To support the hypothesis that the accumulated ***p53*** protein is wild type in most cases, we used single-strand conformation polymorphism analysis and DNA sequencing to evaluate ***p53*** exons 4, 9, and 10 and did not detect mutations at these loci. Although the product of the MDM2 oncogene binds wild type ***p53*** and may account for ***p53*** accumulation, slot-blot analysis of these astrocytomas did not detect MDM2 gene amplification. Thus, evidence suggests that some astrocytomas may accumulate wild type ***p53*** protein but not as a result of MDM2 gene amplification. Furthermore, PAb 1801 immunohistochemistry may not be an adequate method of screening astrocytomas for ***p53*** mutations.

L11 ANSWER 11 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:17099 BIOSIS
DOCUMENT NUMBER: PREV199497030099
TITLE: Increased sequence-specific ***p53*** -DNA binding activity after ***DNA*** ***damage*** is attenuated by phorbol esters.
AUTHOR(S): Price, Brendan D. (1); Calderwood, Stuart K.
CORPORATE SOURCE: (1) Stress Protein Group, Dana-Farber Cancer Inst., 44 Binney St., Boston, MA 02115 USA
SOURCE: Oncogene, (1993) Vol. 8, No. 11, pp. 3055-3062.
ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
AB ***Damage*** to cellular ***DNA*** greatly increases the levels of the ***tumor*** -suppressor gene ***p53*** and induces cell cycle arrest in G-1. A critical function of wild-type ***p53*** is its ability to bind to specific DNA sequences. The effect of ***DNA***

damage on the sequence-specific DNA-binding properties of cellular
p53 was investigated using DNA gel mobility-shift assays with nuclear extracts from NIH3T3 cells. ***DNA*** ***damage*** (initiated by radiation) induced a rapid, cycloheximide-sensitive increase in the levels of nuclear ***p53*** -DNA binding activity and an increase in the half-life of the ***p53*** protein. Increased ***p53*** -DNA binding activity could be detected at low (0.2 Gy), non-lethal doses of radiation. The ***tumor*** promoter 12-O-tetradecanoyl phorbol 13-acetate (TPA) attenuated the ***DNA*** ***damage*** -induced increase in ***p53*** -DNA binding activity by decreasing the half-life of the ***p53*** protein. The ***tumor*** promoter properties of TPA may therefore be mediated by interfering with the cellular ***p53*** response to ***DNA*** ***damage*** . The increased levels of ***p53*** bound to specific ***DNA*** sequences following ***DNA*** ***damage*** may induce cell cycle arrest. ***p53*** -mediated growth arrest could occur by inhibition of DNA replication and/or alterations in transcription of cell cycle genes.

L11 ANSWER 12 OF 82 MEDLINE
ACCESSION NUMBER: 93306625 MEDLINE
DOCUMENT NUMBER: 93306625 PubMed ID: 8319202
TITLE: High frequency of ***p53*** mutations in ultraviolet radiation-induced murine skin ***tumors*** : evidence for strand bias and ***tumor*** heterogeneity.
AUTHOR: Kanjilal S; Pierceall W E; Cummings K K; Kripke M L; Ananthaswamy H N
CORPORATE SOURCE: Department of Immunology, University of Texas M.D. Anderson Cancer Center, Houston 77030.
CONTRACT NUMBER: RO1-CA-46523 (NCI)
RO1-CA-52457 (NCI)
T32-CA-09589 (NCI)
SOURCE: CANCER RESEARCH, ***(1993 Jul 1)*** 53 (13) 2961-4.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930813
Last Updated on STN: 19930813
Entered Medline: 19930730
AB Exposure to UV radiation has long been associated with the development of skin cancers. To identify the molecular targets in UV carcinogenesis, we analyzed 11 UV-induced murine skin cancers for mutations in the ***p53*** ***tumor*** suppressor gene and found a 100% incidence rate. Such a high frequency of ***p53*** mutations is unprecedented and suggests that this gene plays an important role in the development of UV-induced skin cancers. The mutations were predominantly "UV-signature" transitions (C-->T and CC-->TT) at pyrimidine-rich sequences located on the nontranscribed strand of the gene. In addition, seven ***tumors*** harbored multiple mutant alleles of ***p53*** , providing strong evidence for ***tumor*** heterogeneity at the molecular level.

L11 ANSWER 13 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:274315 BIOSIS
DOCUMENT NUMBER: PREV199396004540
TITLE: Mutation of ***p53*** in primary biopsy material and cell lines from Hodgkin disease.
AUTHOR(S): Gupta, Rajnish K. (1); Patel, Ketan; Bodmer, Walter F.; Bodmer, Julia G.
CORPORATE SOURCE: (1) Lab. Tissue Antigen, Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX UK
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1993) Vol. 90, No. 7, pp. 2817-2821.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The ***p53*** ***tumor*** -suppressor gene encodes a nuclear phosphoprotein that arrests cell cycle progress at G-1. It may facilitate ***DNA*** ***damage*** repair and is frequently mutated in many human ***tumors*** . Hodgkin disease, a malignant condition of the lymphoid system, is characterized by the presence of Reed-Sternberg cells and mononuclear variants (Hodgkin cells), whose etiology remains unknown.
The large multinucleated Reed-Sternberg cells often comprise lt 1% of the total cell population within a biopsy specimen and are thought to be the neoplastic component in an admixture of reactive cells. It has been shown in the large majority of cases that up to 60% of these multinucleated cells react with CM-1, an anti- ***p53*** antibody. However, whether this "overexpression" of ***p53*** protein reflects abnormality at the DNA level can no longer be assumed by immunocytochemistry alone. ***p53*** from six Hodgkin disease-derived cell lines was examined by immunoprecipitation, polymerase chain reaction (PCR)-single-strand conformation polymorphism analysis, and sequencing. In one cell line, point mutations were identified in exons 5 and 8 of ***p53*** . Sequencing of cloned PCR products confirmed the mutations to be on different alleles. A strategy involving extraction of nuclei followed by enrichment by flow cytometry was used to determine whether ***p53*** overexpression in the Reed-Sternberg cells from patient biopsy material was due to mutations in this gene. Single-strand conformation polymorphism revealed additional bands in the polyploid nuclear preparations, suggesting abnormalities, and sequence analysis confirmed the presence of point mutations.

L11 ANSWER 14 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93252406 EMBASE
DOCUMENT NUMBER: 1993252406
TITLE: Erratum: Induction of nuclear accumulation of the ***tumor*** -suppressor protein ***p53*** by ***DNA*** - ***damaging*** agents (Oncogene (1993) 8 (307-318)).
AUTHOR: Fritsche; et al.
SOURCE: Oncogene, (1993) 8/9 (2605).
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Errata
FILE SEGMENT: 016 Cancer
LANGUAGE: English

L11 ANSWER 15 OF 82 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:641051 HCAPLUS
DOCUMENT NUMBER: 119:241051
TITLE: Induction of nuclear accumulation of the ***tumor*** -suppressor protein ***p53*** by ***DNA*** - ***damaging*** agents. [Erratum to document cited in CA118(15):139404h]
AUTHOR(S): Fritsche, Michael; Haessler, Christel; Brandner, Gerhard
CORPORATE SOURCE: Inst. Med. Mikrobiol. Hyg., Univ. Freiburg, Freiburg, Germany
SOURCE: Oncogene (***1993***), 8(9), 2605
CODEN: ONCNES; ISSN: 0950-9232
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The errors were not reflected in the abstr. or the index entries.

L11 ANSWER 16 OF 82 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:25645 HCAPLUS
DOCUMENT NUMBER: 120:25645
TITLE: Role of the ***p53*** gene in apoptosis
AUTHOR(S): Takahashi, Rei; Yamamoto, Kanjo; Okuyama, Takazo
CORPORATE SOURCE: Fac. Med., Kyoto Univ., Kyoto, 606, Japan
SOURCE: Jikken Igaku (***1993***), 11(17), 2403-7
CODEN: JIIGEF; ISSN: 0288-5514
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, with 13 refs., on the role of ***p53*** gene in apoptosis in relation to DNA repair, discussing the ***tumor*** suppressing effects

of ***p53*** , cell growth stimulation and apoptosis, ***DNA*** ***damage*** and ***p53*** expression, and apoptosis induction by control of ***p53*** expression.

L11 ANSWER 17 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:322417 BIOSIS
DOCUMENT NUMBER: PREV199396030767
TITLE: Increases in sequence specific DNA binding by ***p53*** following treatment with chemotherapeutic and ***DNA*** ***damaging*** agents.
AUTHOR(S): Tishler, Roy B. (1); Calderwood, Stuart K.; Coleman, C. Norman; Price, Brendan D.
CORPORATE SOURCE: (1) Joint Center Radiation Therapy, 50 Binney St., Boston, MA 02115 USA
SOURCE: Cancer Research, (1993) Vol. 53, No. 10, pp. 2212-2216. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We have investigated the effect of chemotherapeutic and ***DNA*** ***damaging*** agents on binding of the ***tumor*** suppressor phosphoprotein ***p53*** to its consensus DNA sequence. Activation of ***p53*** -DNA binding was seen for treatment with radiation, hydrogen peroxide, actinomycin D, Adriamycin, etoposide, camptothecin, 5-fluorouracil, mitomycin C, and cisplatin. These results showed that DNA strand breaks were sufficient to lead to increased levels of ***p53*** . The protein synthesis inhibitor cycloheximide blocks the increase in ***p53*** following ***DNA*** ***damage*** . The increase in ***p53*** activation in camptothecin treated cells may result, at least in part, from an increased half-life of the protein and consequent increases in intracellular protein concentration.

L11 ANSWER 18 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93311457 EMBASE
DOCUMENT NUMBER: 1993311457
TITLE: ***p53*** mutations in phenacetin-associated human urothelial carcinomas.
AUTHOR: Petersen I.; Ohgaki H.; Ludeke B.I.; Kleihues P.
CORPORATE SOURCE: Institute of Neuropathology, Department of Pathology, University of Zurich,CH-8091 Zurich, Switzerland
SOURCE: Carcinogenesis, (1993) 14/10 (2119-2122). ISSN: 0143-3334 CODEN: CRNGDP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Chronic abuse of the analgesic drug phenacetin is associated with an increased risk of development of transitional cell carcinomas of the urinary tract. It is unclear whether phenacetin acts through chronic tissue damage (phenacetin nephropathy) or via a genotoxic metabolite causing promutagenic DNA lesions. In the present study, we investigated 15 urothelial carcinomas from 13 patients with evidence of phenacetin abuse. ***Tumors*** were screened for ***p53*** mutations in exons 5-8 by single-strand conformation polymorphism (SSCP) analysis, followed by direct sequencing of PCR-amplified DNA. ***p53*** Mutations were detected in 8/14 primary ***tumors*** (57%). All except one were missense mutations located in exon 5 (three mutations), exon 6 (one), exon 7 (two) and exon 8 (one). The type of mutation varied, with a preference for CpG sites. A frameshift mutation resulting from the insertion of a single cytosine at codons 151/152 was detected in a bladder ***tumor*** and its lung metastasis. Urothelial carcinomas located in the renal pelvis and in the ureter of the same patient exhibited two different mutations, strongly suggesting that they developed independently. Another patient had ***tumors*** in the renal pelvis and bladder, both of which contained the same ***p53*** mutation, indicating intracavitary metastatic spread. This demonstrates that screening of ***p53*** mutations allows the clonal origin of ***tumors*** in patients with multiple primary and metastatic lesions to be determined. None of the ***tumors*** investigated contained mutations in codons 12,13 or 61 of H-ras or K-ras protooncogenes.

L11 ANSWER 19 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93304697 EMBASE
DOCUMENT NUMBER: 1993304697
TITLE: The importance of ***p53*** gene alterations in human cancer: Is there more than circumstantial evidence?.
AUTHOR: Frebourg T.; Friend S.H.
SOURCE: Journal of the National Cancer Institute, (1993) 85/19 (1554-1557). ISSN: 0027-8874 CODEN: JNCIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 016 Cancer
022 Human Genetics
LANGUAGE: English

L11 ANSWER 20 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93229715 EMBASE
DOCUMENT NUMBER: 1993229715
TITLE: No allelic loss at the ***p53*** locus in 1,2-dimethylhydrazine-induced mouse colon ***tumors*** : PCR-SSCP analysis with sequence-tagged microsatellite site primers.
AUTHOR: Okamoto M.; Ohtsu H.; Miyaki M.; Yonekawa H.
CORPORATE SOURCE: Dept of Laboratory Animal Science, Tokyo Met Inst of Medical Science, 3-18-22 Honkomagome, Bunkyo-ku,Tokyo 113, Japan
SOURCE: Carcinogenesis, (1993) 14/7 (1483-1486). ISSN: 0143-3334 CODEN: CRNGDP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We examined allelic loss in colon ***tumors*** induced by 1,2-dimethylhydrazine (DMH) in F1 hybrid mice, using sequence-tagged microsatellite site (STMS) primers derived from the chromosomal region closely linked to the ***p53*** locus. Polymerase chain reaction - single-strand conformation polymorphism (PCR-SSCP) analysis of 155 colonic ***tumors*** with two STMS markers revealed that no genetic alterations had occurred in these ***tumors*** , except for one case where one of the markers detected an increase of one CA repeat unit in one allele. No allelic loss at the loci closely linked to the ***p53*** locus strongly suggests that allelic loss at the ***p53*** locus is not involved in DMH-induced colon carcinogenesis in mice.

L11 ANSWER 21 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93317348 EMBASE
DOCUMENT NUMBER: 1993317348
TITLE: Clinical implications of the ***p53*** ***tumor*** -suppressor gene.
AUTHOR: Harris C.C.; Hollstein M.
CORPORATE SOURCE: Laboratory of Human Carcinogenesis, National Cancer Institute, Bldg. 37,Bethesda, MD 20892, United States
SOURCE: New England Journal of Medicine, (1993) 329/18 (1318-1327). ISSN: 0028-4793 CODEN: NEJMAG
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer

022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English

L11 ANSWER 22 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:209208 BIOSIS
DOCUMENT NUMBER: PREV199395110433
TITLE: Distinct pattern of ***p53*** mutations in bladder cancer: Relationship to tobacco usage.
AUTHOR(S): Spruck, Charles H., III; Rideout, William M., III; Olumi, Aria F.; Ohneseit, Petra F.; Yang, Allen S.; Tsai, Yvonne C.; Nichols, Peter W.; Horn, Thomas; Hermann, Gregers G.; et al.
CORPORATE SOURCE: Inq.: Kenneth Norris, Jr., Comprehensive Cancer Cent.,
Univ. Southern Calif., 1441 Eastlake Avenue, Los Angeles, CA 90033-0800
SOURCE: Cancer Research, (1993) Vol. 53, No. 5, pp. 1162-1166.
ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
AB A distinct mutational spectrum for the ***p53*** ***tumor*** suppressor gene in bladder carcinomas was established in patients with known exposures to cigarette smoke. Single-strand conformational polymorphism analysis of exons 5 through 8 of the ***p53*** gene showed inactivating mutations in 16 of 40 (40%) bladder ***tumors*** from smokers and 13 of 40 (33%) ***tumors*** from lifetime nonsmokers.
Overall, 13 of the 50 (26%) total point mutations discovered in this and previous work were G:C fwdarw C:G transversions, a relatively rare mutational type in human ***tumors*** . In six ***tumors*** , identical AGA (Arg) fwdarw ACA (Thr) point mutations at codon 280 were
observed, suggesting a mutational hotspot in these ***tumors*** . Comparison of the mutational spectra from smokers and nonsmokers revealed
no obvious differences in the types or positions of inactivating mutations; however, 5 of 15 ***tumors*** containing point mutations from cigarette smokers had double mutations, four of which were tandem mutations on the same allele. No double mutations were found in ***tumors*** from nonsmoking patients. None of the mutations in smokers
were G:C fwdarw T:A transversions, which would be anticipated for exposure
to the suspected cigarette smoke carcinogen 4-aminobiphenyl. The result suggest that, although cigarette smoke exposure may not significantly alter the kinds of mutations sustained in the ***p53*** gene, it may act to increase the extent of ***DNA*** ***damage*** per mutagenic
event.

L11 ANSWER 23 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93253994 EMBASE
DOCUMENT NUMBER: 1993253994
TITLE: Hematopoietic cells from mice deficient in wild-type ***p53*** are more resistant to induction of apoptosis by some agents.
AUTHOR: Lotem J.; Sachs L.
CORPORATE SOURCE: Dept. of Molecular Genetics/Virology, Weizmann Institute of
Science,Rehovot 76100, Israel
SOURCE: Blood, (1993) 82/4 (1092-1096).
ISSN: 0006-4971 CODEN: BLOOAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Wild-type ***p53*** is a ***tumor*** -suppressor gene that can induce cell death by apoptosis when expressed in myeloid leukemic and some
other types of ***tumor*** cells. However, the question remained as to what extent wild-type ***p53*** is a mediator of apoptosis in normal cells. We have used mice deficient in wild- type ***p53*** to determine whether induction of apoptosis in hematopoietic cells from these
p53 deficient mice is defective. We show here that bone marrow myeloid progenitor cells from ***p53*** -deficient mice are more resistant to induction of apoptosis when there was only a low concentration of the viability factors granulocyte-macrophage colony-stimulating factor; interleukins-1.alpha., -3, and -6; or stem cell factor; or when apoptosis was induced in these cells by irradiation or heat shock. The loss of one allele of wild-type ***p53*** was sufficient for increased resistance. The higher resistance to apoptosis in ***p53*** -deficient mice was also found in irradiated thymocytes, but not in thymocytes treated with dexamethasone or in mature peritoneal granulocytes. The degree of resistance in irradiated myeloid progenitors and thymocytes showed a dosage effect of the number of wild-type ***p53*** genes. The results show that wild-type ***p53*** is involved in the induction of apoptosis by some agents in normal hematopoietic cells. Loss of wild-type ***p53*** can, therefore, contribute to ***tumor*** development by decreasing cell death at low concentrations of viability factors and after exposure to a ***DNA*** - ***damaging*** agent. The results also show that there are wild-type ***p53*** -dependent and -independent pathways of normal cell apoptosis.

L11 ANSWER 24 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93289468 EMBASE
DOCUMENT NUMBER: 1993289468
TITLE: ***p53*** -Dependent apoptosis modulates the cytotoxicity of anticancer agents.
AUTHOR: Lowe S.W.; Ruley H.E.; Jacks T.; Housman D.E.
CORPORATE SOURCE: Department of Biology, Center for Cancer Research,
Massachusetts Inst. of Technology,Cambridge, MA 02139, United States
SOURCE: Cell, (1993) 74/6 (957-967).
ISSN: 0092-8674 CODEN: CELLB5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although the primary cellular targets of many anticancer agents have been
identified, less is known about the processes leading to the selective cell death of cancer cells or the molecular basis of drug resistance. ***p53*** - deficient mouse embryonic fibroblasts were used to examine
systematically the requirement for ***p53*** in cellular sensitivity and resistance to a diverse group of anticancer agents. These results demonstrate that an oncogene, specifically the adenovirus E1A gene, can sensitize fibroblasts to apoptosis induced by ionizing radiation, 5-fluorouracil, etoposide, and adriamycin. Furthermore, the ***p53*** ***tumor*** suppressor is required for efficient execution of the death program. These data reinforce the notion that the cytotoxic action of many anticancer agents involves processes subsequent to the interaction between
drug and cellular target and indicate that divergent stimuli can activate a common cell death program. Consequently, the involvement of ***p53***
in the apoptotic response suggests a mechanism whereby ***tumor*** cells can acquire cross-resistance to anticancer agents.

L11 ANSWER 25 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:342757 BIOSIS
DOCUMENT NUMBER: PREV199396039757
TITLE: ***P53*** is required for radiation induced apoptosis in mouse thymocytes.
AUTHOR(S): Lowe, Scott W. (1); Schmitt, Earlene M. (1); Smith, Sallie
W.; Osborne, Barbara A.; Jacks, Tyler (1)
CORPORATE SOURCE: (1) Dep. Biology, Cent. Cancer Res., Mass. Inst. Technol.,
77 Massachusetts Avenue, Cambridge, MA 02139 USA
SOURCE: Nature (London), (1993) Vol. 362, No. 6423, pp. 847-849.
ISSN: 0028-0836.
DOCUMENT TYPE: Article

LANGUAGE: English
AB The ***p53*** tumour suppressive gene is the most widely mutated gene
in human ***tumorigenesis*** . ***p53*** encodes a transcriptional activator whose targets may include genes that regulate genomic stability, the cellular response to ***DNA*** ***damage*** , and cell-cycle progression. Introduction of wild-type ***p53*** into cell lines that have lost endogenous ***p53*** function can cause growth arrest induce
a process of cell death known as apoptosis. During normal development, self-reactive thymocytes undergo negative selection by apoptosis, which also an be induced in immature thymocytes by other stimuli, including exposure to glucocorticoids and ionizing radiation. Although normal negative selection involves signalling through the T-cell receptor, the induction of apoptosis by other stimuli is poorly understood. We have investigated the requirement for ***p53*** during apoptosis in spouse thymocytes. We report here that immature thymocytes lacking ***p53***
die normally when exposed to compounds that may mimic T-cell receptor engagement and to glucocorticoids but are resistant to the lethal effects of ionizing radiation. These results demonstrate that ***p53*** is required for radiation-induced cell death in the thymus but is not necessary for all forms of apoptosis.

L11 ANSWER 26 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:230481 BIOSIS
DOCUMENT NUMBER: PREV199395121656
TITLE: Structure of the rat ***p53*** ***tumor*** suppressor gene.
AUTHOR(S): Hulla, Janis E.; Schneider, Richard P.
CORPORATE SOURCE: Pacific Northwest Lab., Box 999, MSIN P7-56, Richland, WA
99352
SOURCE: Nucleic Acids Research, (1993) Vol. 21, No. 3, pp. 713-717.
ISSN: 0305-1048.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Aberration within the p54 ***tumor*** suppressor gene is the most frequently identified genetic damage in human cancer. Regulatory functions
proposed for the ***p53*** protein include modulation of the cell cycle, cellular differentiation, signal transduction, and gene expression. Additionally, the ***p53*** gene product may guard the genome against
incorporation of ***damaged*** ***DNA*** . To facilitate study of its role in carcinogenesis using a common animal model, we determined the
structure of the rat ***p53*** gene. We identified 18 splice sites and defined 25 bases of the intervening sequences adjacent to these sites. We also discovered an allelic polymorphism that occurs within intron 5 of the gene. The rat gene approximates the mouse ortholog. It is 12 kb in length with the non-coding exon 1 separated from exon 2 by 6.2 kb in intervening sequence. The location and size of all rat gene introns approximate those of the mouse. Whereas the mouse and human gene each contain 11 exons, the
rat ***p53*** gene is composed of only 10. No intervening sequence occurs between the region of the rat gene corresponding to exons 6 and 7 of the mouse and human ***p53*** genes. This implies intron 6 may be functionally insignificant for species in which it is retained. To extrapolate to ***p53*** involvement in human ***tumorigenesis*** ,
we suggest that involvement in human ***tumorigenesis*** , we suggest that mutational events within intron 6 may not be of pathological significance, unless splicing is hindered.

L11 ANSWER 27 OF 82 MEDLINE
ACCESSION NUMBER: 93109358 MEDLINE
DOCUMENT NUMBER: 93109358 PubMed ID: 8417361
TITLE: Cell cycle analysis of ***p53*** -induced cell death in murine erythroleukemia cells.
AUTHOR: Ryan J J; Danish R; Gottlieb C A; Clarke M F
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan
Medical Center, Ann Arbor 48109-0668.
CONTRACT NUMBER: CA-46657 (NCI)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, ***(1993 Jan)*** 13 (1)
711-9.
Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199301
ENTRY DATE: Entered STN: 19930212
Last Updated on STN: 19970203
Entered Medline: 19930127
AB A temperature-sensitive mutant of murine ***p53*** (p53Val-135) was
transfected by electroporation into murine erythroleukemia cells (DP16-1) lacking endogenous expression of ***p53*** . While the transfected cells grew normally in the presence of mutant ***p53*** (37.5 degrees C), wild-type ***p53*** (32.5 degrees C) was associated with a rapid loss of cell viability. Genomic DNA extracted at 32.5 degrees C was seen to be fragmented into a characteristic ladder consistent with cell death due to apoptosis. Following synchronization by density arrest, transfected cells released into G1 at 32.5 degrees C were found to lose viability more rapidly than did randomly growing cultures. Following release into G1, cells became irreversibly committed to cell death after 4 h at 32.5 degrees C. Commitment to cell death correlated with the first appearance of fragmented DNA. Synchronized cells allowed to pass out of G1 prior to being placed at 32.5 degrees C continued to cycle until subsequently arrested in G1; loss of viability occurred following G1 arrest. In contrast to cells in G1, cells cultured at 32.5 degrees C for prolonged periods during S phase and G2/M, and then returned to 37.5 degrees C, did
not become committed to cell death. G1 arrest at 37.5 degrees C, utilizing either mimosine or isoleucine deprivation, does not lead to rapid cell death. Upon transfer to 32.5 degrees C, these G1 synchronized cell populations quickly lost viability. Cells that were kept density arrested at 32.5 degrees C (G0) lost viability at a much slower rate than did cells released into G1. Taken together, these results indicate that wild-type ***p53*** induces cell death in murine erythroleukemia cells and that this effect occurs predominantly in the G1 phase of actively cycling cells.

L11 ANSWER 28 OF 82 MEDLINE
ACCESSION NUMBER: 94011527 MEDLINE
DOCUMENT NUMBER: 94011527 PubMed ID: 8406999
TITLE: Increased accumulation of ***p53*** protein in cisplatin-resistant ovarian cell lines.
AUTHOR: Brown R; Clugston C; Burns P; Edlin A; Vasey P; Vojtesek B;
Kaye S B
CORPORATE SOURCE: CRC Dept. Medical Oncology, CRC Beatson Laboratories,
Garscube Estate, Bearsden, Glasgow, UK.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, ***(1993 Oct 21)*** 55
(4) 678-84.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19970203
Entered Medline: 19931122
AB We have examined ***p53*** protein levels in cell lines selected for resistance to the chemotherapeutic drug cis-diamminedichloroplatinum (II), cisplatin. The majority of the independent cisplatin-resistant clones isolated by a single selection with cisplatin from the ovarian tumour cell line A2780 showed increased levels of ***p53*** protein compared to the parental cell line. Elevated ***p53*** protein levels were also observed in cisplatin-resistant ovarian human tumour lines isolated after multiple exposures to cisplatin (A2780/cp70 and OVIP/DDP). Direct PCR sequencing of ***p53*** cDNAs showed that both the A2780/cp70 and the
parental A2780 cell lines had a wild-type ***p53*** gene sequence. The
OVIP and OVIP/DDP lines both had a heterozygous mutation at codon 126.
Cell-cycle analysis after gamma-irradiation or cisplatin treatment showed

evidence of a G1/S and G2/M cell-cycle checkpoint in both A2780/cp70 and
the sensitive parental cell lines. However, the resistant cell line A2780/cp70 showed less inhibition of DNA synthesis after gamma-irradiation
than the sensitive cell line. Transfection of a mutant ***p53*** gene construct (containing a mutation at codon 143, val to ala) into the A2780/cp70 resistant cells conferred a significantly increased sensitivity to cisplatin, suggesting that ***p53*** is a direct determinant of cisplatin resistance in these cells. However, expression of this mutant ***p53*** in the A2780 cells did not affect sensitivity.

L11 ANSWER 29 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94209261 EMBASE
DOCUMENT NUMBER: 1994209261
TITLE: Cell cycle regulation of gene amplification.
AUTHOR: Di Leonardo A.; Linke S.P.; Yin Y.; Wahl G.M.
CORPORATE SOURCE: Gene Expression Laboratory, Salk Institute,San Diego, CA
92037, United States
SOURCE: Cold Spring Harbor Symposia on Quantitative Biology, (1993)
58/- (655-667).
ISSN: 0091-7451 CODEN: CSHSAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 021 Developmental Biology and Teratology
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English

L11 ANSWER 30 OF 82 MEDLINE
ACCESSION NUMBER: 93209539 MEDLINE
DOCUMENT NUMBER: 93209539 PubMed ID: 8384580
TITLE: Wild-type ***p53*** mediates apoptosis by E1A, which is
inhibited by E1B.
AUTHOR: Debbas M; White E
CORPORATE SOURCE: Center for Advanced Biotechnology and Medicine, Rutgers
University, Piscataway, New Jersey 08854.
CONTRACT NUMBER: CA53370 (NCI)
SOURCE: GENES AND DEVELOPMENT, ***(1993 Apr)*** 7 (4) 546-54.
Journal code: FN3; 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930514
Last Updated on STN: 19930514
Entered Medline: 19930429
AB Transformation of primary rodent cells by the adenovirus E1A and E1B oncogenes is a two-step process, where E1A-dependent induction of proliferation is coupled to E1B-dependent suppression of programmed cell death (apoptosis). The E1B gene encodes two distinct transforming proteins, the 19K and 55K proteins, both of which independently cooperate
with E1A. E1B 19K or 55K protein, or the human Bcl-2 protein, functions to
suppress apoptosis and thereby permits transformation with E1A. The E1B
55K protein blocks ***p53*** ***tumor*** suppressor protein function, indicating that ***p53*** may mediate apoptosis by E1A. In the mutant conformation, ***p53*** blocked induction of apoptosis by E1A and efficiently cooperated with E1A to transform primary cells. When
p53 was returned to the wild-type conformation, E1A+ ***p53***
transformants underwent cell death by apoptosis. This induction of apoptosis by conformational shift of ***p53*** from the mutant to the wild-type form was inhibited by expression of the E1B 19K protein. Thus, the ***p53*** protein may function as a ***tumor*** suppressor by initiating a cell suicide response to deregulation of growth control by E1A. E1B 19K and 55K proteins provide separate mechanisms that disable the
cell suicide pathway of ***p53*** .

L11 ANSWER 31 OF 82 MEDLINE
ACCESSION NUMBER: 93209537 MEDLINE
DOCUMENT NUMBER: 93209537 PubMed ID: 8096197
TITLE: The ***p53*** ***tumor*** suppressor protein: meeting review.
AUTHOR: Prives C; Manfredi J J
CORPORATE SOURCE: Department of Biological Sciences, Columbia University, New
York 10027.
SOURCE: GENES AND DEVELOPMENT, ***(1993 Apr)*** 7 (4) 529-34.
Journal code: FN3; 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
Conference; Conference Article; (CONGRESSES)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930514
Last Updated on STN: 19990129
Entered Medline: 19930429

L11 ANSWER 32 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:501723 BIOSIS
DOCUMENT NUMBER: PREV199396125730
TITLE: Analysis of G418-selected Rat2 cells containing prototype, variant, mutant, and chimeric JC virus and SV40 genomes.
AUTHOR(S): Trowbridge, Pamela W.; Frisque, Richard J. (1)
CORPORATE SOURCE: (1) Dep. Molecular Cell Biology, Pa. State Univ., University Park, PA 16802 USA
SOURCE: Virology, (1993) Vol. 196, No. 2, pp. 458-474.
ISSN: 0042-6822.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The human polyomavirus JC virus (JCV) is highly ***tumorigenic*** in
rodents, but transforms cells in culture inefficiently. To explore the basis for JCV's restricted transforming behavior, nonpermissive Rat2 cells were cotransfected with pSV2-neo (encodes G418 resistance) and viral DNAs
including prototype, variant, and mutant JCV genomes and two JCV-SV40
chimeras. By selecting cells displaying G418 resistance, lines were established that contain viral DNA and exhibit a wide range of transformed
phenotypes. The G418-resistant lines were tested for their ability to grow under anchorage-independent conditions, to overgrow a monolayer of untransformed cells, and to form dense colonies on plastic. Expression of the viral T and t proteins and interaction of T protein with the cellular anti-oncoprotein ***p53*** were measured. Also determined was the number of intact viral early coding regions integrated within the cellular DNA. The results of these studies suggested that most of the G418-resistant lines failed to express JCV T protein above a minimum threshold level required for their conversion to a fully transformed phenotype. In anchorage-independent growth assays, higher levels of a 17-kDa T-related peptide in JCV transformants appeared to compensate for
decreased T antigen levels. Comparisons of the T to ***p53*** ratios in the cell lysates suggested that the quaternary structure of the JCV protein differed from that of its SV40 counterpart in the T- ***p53*** complex. The presence of multiple vs single integrated copies of the viral genome in the cells did not correlate with elevated T antigen expression or an enhanced transformation status.

L11 ANSWER 33 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93316643 EMBASE
DOCUMENT NUMBER: 1993316643
TITLE: ***DNA*** ***damage*** and the ***DNA*** -activated protein kinase.
AUTHOR: Anderson C.W.
CORPORATE SOURCE: Biology Department, Brookhaven National Laboratory,Upton,
NY 11973-5000, United States
SOURCE: Trends in Biochemical Sciences, (1993) 18/11 (433-437).
ISSN: 0968-0004 CODEN: TBSCDB
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB DNA-activated protein kinase (DNA-PK) is a nuclear serine/threonine protein kinase that is activated in vitro by DNA fragments. The cellular targets of DNA-PK are nuclear, DNA-binding, regulatory proteins including Sp1, Fos, Jun, Myc, the ***tumor*** suppressor protein ***p53*** , and RNA polymerase II. These characteristics suggest a role for DNA-PK in coordinating nuclear processes and as a modulator of checkpoint mechanisms activated by ***DNA*** ***damage*** .

L11 ANSWER 34 OF 82 MEDLINE
ACCESSION NUMBER: 94331816 MEDLINE
DOCUMENT NUMBER: 94331816 PubMed ID: 8054700
TITLE: ***DNA*** ***damage*** , gene expression, growth arrest and cell death.
AUTHOR: Gewirtz D A
CORPORATE SOURCE: Department of Medicine, Medical College of Virginia, Richmond 23298.
SOURCE: ONCOLOGY RESEARCH, ***(1993)*** 5 (10-11) 397-408.
Ref: 153
Journal code: BBN; 9208097. ISSN: 0965-0407.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19940920
Last Updated on STN: 19940920
Entered Medline: 19940912
AB The sequence of biochemical and molecular events that mediate growth arrest and cell death in ***tumor*** cells exposed to agents that induce ***DNA*** ***damage*** is poorly defined. This commentary exploits the recent explosion of information regarding oncogenes, ***tumor*** suppressor genes, and cell-cycle regulatory genes to develop a model for growth arrest/cell death. The model focuses on changes in the expression of these genes, in the level and phosphorylation of their protein products, and in the interaction(s) between these proteins. It is recognized that such a model is, of necessity, incomplete, since new gene functions associated with the cellular response to ***DNA*** ***damage*** will continuously be uncovered; in addition, the proposed sequence of events will likely require modification as the relationships between the functions of the discrete gene products are clarified. Nevertheless, it is hoped that this commentary will provide a conceptual framework within which to fit currently available information as well as future findings relating to the expression and function of ***DNA*** - ***damage*** -responsive genes, and that the sections of the model that are incomplete will provide a springboard for the development of research approaches designed to answer specific questions regarding the nature of the cellular response to ***DNA*** ***damage*** .

L11 ANSWER 35 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:253841 BIOSIS
DOCUMENT NUMBER: PREV199395133016
TITLE: Tumour induction in mouse epidermal cells irradiated by hot particles.
AUTHOR(S): Lang, S.; Kosma, V.-M.; Servomaa, K.; Ruuskanen, J.; Rytomaa, T. (1)
CORPORATE SOURCE: (1) Dep. Res., Finnish Centre Radiation Nuclear Safety, P.O. Box 268, 00101 Helsinki Finland
SOURCE: International Journal of Radiation Biology, (1993) Vol. 63, No. 3, pp. 375-381.
ISSN: 0955-3002.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We have shown elsewhere that highly non-uniform exposure to ionizing radiation from authentic Chernobyl-released and artificially-produced hot particles (fragments of nuclear fuel) transform fibroblastic 10T1/2 cells in vitro effectively. We have also shown that hot-particle exposure leads to mutation and overexpression of the ***tumor*** suppressor gene ***p53*** (and some other growth-related genes) in mouse skin in vivo at a high frequency. In the present paper it is shown that hot particles produced by irradiating natural uranium with slow neutrons, when implanted (immobilized) under the skin of hairless and nude mice, induce epidermal tumours in excess compared with the conventional non-threshold stochastic model of radiation-induced cancer. One explanation for the effectiveness of the hot-particle exposure, under the present assay conditions, is that the same cells in which specific radiation-induced ***DNA*** ***damage*** is most likely to occur, are forced into sustained mitotic activity in the chronic wound which develops around the radiation source (combined genotoxic and nongenotoxic effects). The results are consistent with a role for cell proliferation in multistage carcinogenesis in mouse skin.

L11 ANSWER 36 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:163221 BIOSIS
DOCUMENT NUMBER: PREV199497176221
TITLE: The biology of radioresistance: Similarities, Differences and interactions with drug resistance.
AUTHOR(S): Powell, Simon N. (1); Abraham, Edward H.
CORPORATE SOURCE: (1) Dep. Radiation Oncol., Mass. Gen. Hosp., Boston, MA 02114 USA
SOURCE: Cytotechnology, (1993) Vol. 12, No. 1-3, pp. 325-345.
ISSN: 0920-9069.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Cells and tissues have developed a variety of ways of responding to a hostile environment, be it from drugs (toxins) or radiation. Three categories of radiation ***damage*** limitation are: (i) ***DNA*** repair (ii) changes in cellular metabolism (iii) changes in cell interaction (cell contact or tissue-based resistance; whole organism based resistance). DNA repair has been evaluated predominantly by the study of repair-deficient mutants. The function of the repair genes they lack is not fully understood, but some of their important interactions are now characterized. For example, the interaction of transcription factors with nucleotide excision repair is made clear by the genetic syndromes of xeroderma-pigmentosum groups B, D and G. These diseases demonstrate ultraviolet light sensitivity and general impairment of transcription: they are linked by impaired unwinding of the DNA required for both transcription and repair. The transfer of DNA into cells is sometimes accompanied by a change in sensitivity to radiation, and this is of special interest when this is the same genetic change seen in ***tumors*** . DNA repair has a close relationship with the cell cycle and cell cycle arrest in response to damage may determine sensitivity to that ***damage*** . ***DNA*** repair mechanisms in response to a variety of drugs and types of radiation can be difficult to study because of the inability to target the damage to defined sequences in vivo and the lack of a satisfactory substrate for in vitro studies. Changes in cellular metabolism as a result of ionizing radiation can impart radiation resistance, which is usually transient in vitro, but may be more significant in vivo for tissues or ***tumors*** . The mechanisms by which damage is sensed by cells is unknown. The detection of free radicals is thought likely, but distortion to DNA structure or strand breakage and a direct effect on membranes are other possibilities for which there is evidence. Changes in extracellular ATP occur in response to damage, and this could be a direct membrane effect. External purinergic receptors can then be involved in signal transduction pathways resulting in altered levels of thiol protection or triggering apoptosis. Changes in the functional level of proteins as a consequence of ionizing radiation include transcription factors, for example c-jun and c-fos; cell cycle arrest proteins such as GADD (growth arrest and ***DNA*** ***damage*** inducible proteins) and ***p53*** ; growth factors such as FGF, PDGF; and other proteins leading to radioresistance. Mechanisms for intercellular resistance could be mediated by cell contact, such as gap junctions, which may help resistance to radiation in non-cycling cells. Paracrine response mechanisms, such as the release of angiogenic factors via membrane transport channels may account for tissue and ***tumor*** radiation resistance. Endocrine response mechanisms may

also
contribute to tissue or ***tumor*** resistance.

L11 ANSWER 37 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:63975 BIOSIS
DOCUMENT NUMBER: PREV199497076975
TITLE: Point mutations of the ***P53*** gene, human hepatocellular carcinoma and aflatoxins.
AUTHOR(S): Gerbes, Alexander L. (1); Caselmann, Wolfgang H.
CORPORATE SOURCE: (1) Dep. Med. II, Klinikum Grosshadern, Univ. Munich, Marchioninistr. 15, 81366 Munich Germany
SOURCE: Journal of Hepatology, (1993) Vol. 19, No. 2, pp. 312-315.
ISSN: 0168-8278.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB The ***tumor*** suppressor ***p53*** exerts important protective functions towards ***DNA*** - ***damaging*** agents. Its inactivation by allelic deletions or point mutations within the ***P53*** gene as well as complex formation of wildtype ***p53*** with cellular or viral proteins is a common and crucial event in carcinogenesis. Mutations increase the half-life of the ***p53*** protein allowing the immunohistochemical detection and anti- ***p53*** antibody formation. Distinct G to T point mutations in codon 249 leading to a substitution of the basic amino acid arginine by the neutral amino acid serin are responsible for the altered functionality of the mutant gene product and were originally identified in 8 of 16 Chinese and 5 of 10 African HCC patients. Both groups are frequently exposed to mycotoxin contaminations of their food. Today an average ***P53*** gene mutation rate of 25% is assumed for high-aflatoxin B-1-exposure regions. This is double the rate observed in low-aflatoxin B-1-exposure countries. Although many HCC patients displaying ***P53*** mutations also suffer from HBV infection, which itself can lead to rearrangements of ***P53*** coding regions or induce the synthesis of viral proteins possibly interacting with ***p53*** , the specific G to T transversion within codon 249 of the ***P53*** gene seems to directly reflect the extent of aflatoxin B-1 exposure.

L11 ANSWER 38 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:166759 BIOSIS
DOCUMENT NUMBER: PREV199395087809
TITLE: Induction of nuclear accumulation of the ***tumor*** -suppressor protein ***p53*** by ***DNA*** - ***damaging*** agents.
AUTHOR(S): Fritsche, Michael; Haessler, Christel; Brandner, Gerhard (1)
CORPORATE SOURCE: (1) Abteilung Virologie, Inst. fuer Medizinische Mikrobiologie und Hygiene der Universitaet, P.O.B. 820, D78 Freiburg Germany
SOURCE: Oncogene, (1993) Vol. 8, No. 2, pp. 307-318.
ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Cancer therapy drugs, such as diamminedichloroplatinum (cisplatin), mitomycin C, etoposide and a number of other compounds, as well as energy-rich radiation, are known to act on cellular DNA. These agents are shown to induce nuclear accumulation of the so-called ***tumor*** -suppressor protein ***p53*** in fibroblastoid cells, as well as in epithelioid normal and immortalized cells of murine, simian, and human origin. ***p53*** accumulation starts a few hours after treatment and can remain detectable in surviving cells for at least 20 days. Accumulation occurs because of increased ***p53*** protein stability and depends on ongoing translation. It is not the result of enhanced gene expression. A number of cell cycle inhibitors do not affect ***p53*** protein accumulation, suggesting that the process may start from several points in the cell cycle. Since the increase in the nuclear ***p53*** protein levels occurs within a few hours in most of the treated normal diploid cells, it is unlikely that the accumulated ***p53*** protein is derived from a mutated ***p53*** gene. The results obtained are in accordance with the view that the ***DNA*** ***damage*** -induced ***p53*** accumulation may either inhibit cell growth, allowing DNA repair process, or, in the case of severe damage, initiate apopotosis.

L11 ANSWER 39 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94066663 EMBASE
DOCUMENT NUMBER: 1994066663
TITLE: Discussion of Dr. Kastan's presentation.
AUTHOR: Moran; Kastan M.B.; DeCabrio; Mihich E.; Kufe
SOURCE: Advances in Experimental Medicine and Biology, (1993) 339/- (295-296).
ISSN: 0065-2598 CODEN: AEMBAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English

L11 ANSWER 40 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94066662 EMBASE
DOCUMENT NUMBER: 1994066662
TITLE: ***p53*** : A determinant of the cell cycle response to ***DNA*** ***damage*** .
AUTHOR: Kastan M.B.
CORPORATE SOURCE: Johns Hopkins Oncology Center,Baltimore, MD 21287, United States
SOURCE: Advances in Experimental Medicine and Biology, (1993) 339/- (291-293).
ISSN: 0065-2598 CODEN: AEMBAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English

L11 ANSWER 41 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93226782 EMBASE
DOCUMENT NUMBER: 1993226782
TITLE: Does a genotoxic carcinogen contribute to human breast cancer? The value of mutational spectra in unravelling the aetiology of cancer.
AUTHOR: Biggs P.J.; Warren W.; Venitt S.; Stratton M.R.
CORPORATE SOURCE: Section of Molecular Carcinogenisis, Institute of Cancer Research, 15 Cotswold Road,Belmont, Sutton SM2 5NG, United Kingdom
SOURCE: Mutagenesis, (1993) 8/4 (275-283).
ISSN: 0267-8357 CODEN: MUTAEX
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The ***p53*** tumour suppressor gene is turning out to be a useful reporter for the stigmata of past genotoxic exposure. About half of all human cancers contain ***p53*** mutations most of which occur in those regions (exons 5-8) of the gene that are highly conserved during evolution. Mutations are mainly of the missense type and their frequency and distribution vary among different kinds of cancer. The ability to detect all six possible base-substitution mutations in the ***p53*** gene in human tumours makes it possible to construct mutational spectra for different cancers at a locus clearly implicated in carcinogenesis. Transitions at one particular hotspot - the CpG dinucleotide - occur frequently in many cancers and may reflect endogenous mutation. A reduction in the proportion of CpG mutations at the expense, for example, of an increase in GC to TA transversions may signal the effect of an exogenous mutagen. We exploited these features of the ***p53*** gene to examine the evidence that a previously unsuspected genotoxic exposure may contribute to the high incidence of breast cancer in women living in rich industrialized countries. We compiled a mutational spectrum of ***p53*** from 120 breast cancers and compared it with the spectrum from 145 colorectal cancers and 246 lung cancers. A germline ***p53***

spectrum was constructed using data from 27 patients. Two hundred germline
mutations in the haemophilia B gene served as a 'background' spectrum. The
spectrum of mutations in the ***p53*** gene in breast cancer revealed a reduction in the proportion of G - A and C - T transitions at CpG
dinucleotides compared with colorectal cancer ($P < 0.0005$) and an increase
in G - T transversions ($P < 0.0005$). Other mutations showed no significant
differences from colorectal cancer or germline mutational spectra. In breast cancer, as in lung cancer, G - T transversions were over-represented at CpG dinucleotides and there was also a G - T hotspot at codon 157 that was not seen in colorectal cancer. Moreover, G - T transversions were much more common on the coding strand, as in lung cancer. Thus, the mutational spectrum in the ***p53*** gene of breast cancer differs significantly from that thought to be attributable to endogenous or background mutagenic processes. It resembles more closely
the lung cancer spectrum, which is probably caused by exogenous mutagenic
chemicals. These findings pose the following questions. Is a mutagenic agent of exogenous or endogenous origin involved in the aetiology of breast cancer? Is the breast epithelium and/or its neoplastic derivatives less efficient at repairing ***DNA*** ***damage*** than are colorectal epithelial cells?

L11 ANSWER 42 OF 82 MEDLINE
ACCESSION NUMBER: 94189169 MEDLINE
DOCUMENT NUMBER: 94189169 PubMed ID: 7511292
TITLE: [***p53*** mutation in phenacetin-induced urothelial carcinomas].
p53 Mutationen in Phenazetin-induzierten Urothelkarzinomen.
AUTHOR: Petersen I; Ohgaki H; Ludeke B I; Kleihues P
CORPORATE SOURCE: Institut fur Neuropathologie, Departement Pathologie,
Zurich.
SOURCE: VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FUR PATHOLOGIE,
(1993) 77 252-5.
Journal code: X8G; 7503704. ISSN: 0070-4113.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940509
Last Updated on STN: 19980206
Entered Medline: 19940425
AB We investigated 16 urothelial carcinomas from 13 patients with evidence of
phenacetin abuse for ***p53*** mutations by single-strand conformation
polymorphism (SSCP) analysis and direct DNA sequencing. ***p53*** mutations were detected in 8 of 14 primary ***tumors*** (57%). Missense mutations were located in exon 5 (3 mutations), exon 6 (1), exon 7 (2) and exon 8 (1). An insertion of a single cytosine in exon 5 was detected in a bladder ***tumor*** and its lung metastasis. In one patient, urothelial carcinomas in the renal pelvis and in the ureter exhibited two different mutations, strongly suggesting that these ***tumors*** developed independently. In contrast, the ***tumors*** in the renal pelvis and bladder of another patient contained the same mutation, indicating intracavitary metastatic spread. Our data support the view that phenacetin causes urothelial carcinomas through chronic tissue ***damage*** rather than promutagenic ***DNA*** lesions.

L11 ANSWER 43 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:312763 BIOSIS
DOCUMENT NUMBER: PREV199345019288
TITLE: ***P53*** -Deficient embryonic fibroblasts exhibit decreased sensitivity to ***DNA*** ***damage*** and altered cell cycle control.
AUTHOR(S): Sands, Arthur T.; Donehower, Lawrence A.; Bradley, Allan
CORPORATE SOURCE: Dep. Molecular Genetics, Baylor Coll. Med., Houston, TX
77030 USA
SOURCE: Journal of Cellular Biochemistry Supplement, (1993) Vol. 0,
No. 17 PART E, pp. 246.
Meeting Info.: Keystone Symposium on Gene Therapy Keystone,
Colorado, USA April 12-18, 1993
ISSN: 0733-1959.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 44 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94024300 EMBASE
DOCUMENT NUMBER: 1994024300
TITLE: Molecular mechanisms in cancer induction and prevention.
AUTHOR: Borek C.
CORPORATE SOURCE: Div of Radiation and Cancer Biology, Dept Radiat Oncol
Tufts Univ Sch Med, and New England Medical Center,Boston, MA 02111, United States
SOURCE: Environmental Health Perspectives, (1993) 101/SUPPL. 3 (237-245).
ISSN: 0091-6765 CODEN: EVHPAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
017 Public Health, Social Medicine and Epidemiology
022 Human Genetics
037 Drug Literature Index
046 Environmental Health and Pollution Control
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Chemical and physical carcinogens, present in our environment and encountered in a variety of occupations, produce ***damage*** to ***DNA*** . X-rays produce directionizations and indirect hydroxyl radical attack. UV light in the short wavelength is specifically absorbed by unsaturated bonds in DNA, RNA, and proteins. There are a number of genetic sites that are specifically affected by environmental agents, and an increased sensitivity is found in certain genetic diseases. The development of a fully malignant ***tumor*** involves the activation or altered expression of oncogenes or the inactivation of ***tumor*** -suppressor genes that control normal cellular development. Mutations in the ***p53*** ***tumor*** -suppressor gene are common in diverse types of cancer and could perhaps provide clues to the etiology of some cancers and to the effect of various environmental and occupational carcinogens in cancer development. The fact that environmental factors are
involved to a great extent in cancer suggest that cancer may be preventable. Experimental as well as epidemiological data indicate that a variety of nutritional factors can act as anticarcinogens and inhibit the process of cancer development and reduce cancer risk. The interaction of cells with a number of environmental and occupational genotoxic substances
such as X-rays, UV light, and a variety of chemicals including ozone results in an enhanced generation of free oxygen radicals and in modified pro-oxidant states. A number of nutritional factors such as vitamins A, C, E, .beta.-carotene, and micronutrients such as selenium act as antioxidants and anticarcinogens. Certain hormones such as thyroid hormones enhance oxidative processes and act as a co-transforming factor in carcinogenesis. A number of bioactive lipids act as cancer preventive agents. Sphingolipids act on signal transduction pathways and inhibit protein kinase C and multistep carcinogenesis. Sphingolipids are found in dairy products and milk. .omega.-3 fatty acids suppress X-ray induced transformation as well as promotion. They also inhibit transformation by the ras oncogene. The .omega.-3 fatty acids act in part by reducing prostaglandin synthesis. In addition, the ?-3 fatty acids alter the composition of membrane fatty acids that are released from one or more phospholipids, causing remodeling of cellular phospholipids and reduced arachidonate-containing species. Such remodeling interferes with transformation.

L11 ANSWER 45 OF 82 MEDLINE
ACCESSION NUMBER: 93319678 MEDLINE
DOCUMENT NUMBER: 93319678 PubMed ID: 8329141
TITLE: 11th Ernst Klenk Lecture. The ***p53*** ***tumor*** suppressor gene and product.
AUTHOR: Levine A J

CORPORATE SOURCE: Department of Molecular Biology, Lewis Thomas Laboratory,
Princeton University, NJ 08544-1014.
SOURCE: BIOLOGICAL CHEMISTRY HOPPE-SEYLER, ***(1993 Apr)*** 374
(4) 227-35. Ref: 99
Journal code: AHC; 8503054. ISSN: 0177-3593.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 19930826
Last Updated on STN: 19930826
Entered Medline: 19930816

L11 ANSWER 46 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:435497 BIOSIS
DOCUMENT NUMBER: PREV199497448497
TITLE: Mice with DNA repair gene (ERCC-1) deficiency have elevated
levels of ***p53*** , liver nuclear abnormalities and die before weaning.
AUTHOR(S): McWhir, Jim; Selfridge, Jim; Harrison, David J.; Squires,
Shoshana; Melton, David W. (1)
CORPORATE SOURCE: (1) Inst. Cell and Molecular Biol., Univ. Edinburgh,
Mayfield Road, Edinburgh EH9 3JR UK
SOURCE: Nature Genetics, (1993) Vol. 5, No. 3, pp. 217-224.
ISSN: 1061-4036.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Defects in nucleotide excision repair are associated with the human condition xeroderma pigmentosum which predisposes to skin cancer. Mice with defective DNA repair were generated by targeting the excision repair cross complementing gene (ERCC-1) in the embryonic stem cell line, HM-1.
Homozygous ERCC-1 mutants were runted at birth and died before weaning
with liver failure. Examination of organs revealed polyploidy in perinatal liver, progressing to severe aneuploidy by 3 weeks of age. Elevated ***p53*** levels were detected in liver, brain and kidney, supporting the hypothesised role for ***p53*** as a monitor of ***DNA*** ***damage*** .

L11 ANSWER 47 OF 82 MEDLINE
ACCESSION NUMBER: 93283162 MEDLINE
DOCUMENT NUMBER: 93283162 PubMed ID: 8507493
TITLE: Doing the right thing: feedback control and ***p53*** .
AUTHOR: Prives C
CORPORATE SOURCE: Department of Biological Sciences, Columbia University, New
York, New York 10027.
CONTRACT NUMBER: CA33620 (NCI)
SOURCE: CURRENT OPINION IN CELL BIOLOGY, ***(1993 Apr)*** 5 (2)
214-8. Ref: 54
Journal code: AOE; 8913428. ISSN: 0955-0674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930723
Last Updated on STN: 19930723
Entered Medline: 19930713
AB Recent evidence suggests that exposure of cells to ***DNA*** - ***damaging*** agents causes a rise in the levels of the ***p53*** ***tumor*** suppressor protein and arrest of progression through the cell cycle. ***p53*** may therefore resemble a member of the RAD gene
class identified in yeast, RAD9, which allows cells to repair DNA before continuation of the cell cycle. The evidence that ***p53*** is a sequence-specific, DNA-binding protein that can regulate transcription suggests several ways in which ***p53*** might effect this growth cessation.

L11 ANSWER 48 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:517824 BIOSIS
DOCUMENT NUMBER: PREV199345116449
TITLE: ***DNA*** ***damaging*** agents increase sequence specific DNA binding by ***p53*** .
AUTHOR(S): Tishler, Roy B.; Calderwood, Stuart K.; Coleman, C. Norman;
Price, Brendan D.
CORPORATE SOURCE: Joint Center Radiation Therapy, 50 Binney St., Boston, MA
02115 USA
SOURCE: International Journal of Radiation Oncology Biology Physics, (1993) Vol. 27, No. SUPPL. 1, pp. 211-212.
Meeting Info.: 35th Annual Meeting of the American Society for Therapeutic Radiology and Oncology New Orleans, Louisiana, USA October 11-15, 1993
ISSN: 0360-3016.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 49 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:166327 BIOSIS
DOCUMENT NUMBER: PREV199395087377
TITLE: High levels of ***p53*** protein in UV-irradiated normal human skin.
AUTHOR(S): Hall, Peter A. (1); McKee, Philip H.; Menage, Helene D.;
Dover, Robin; Lane, David P.
CORPORATE SOURCE: (1) Dep. Histopathology, UMDS, St. Thomas's Campus, Lambeth
Palace Road, London SE1 7EH UK
SOURCE: Oncogene, (1993) Vol. 8, No. 1, pp. 203-207.
ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Exposure of normal adult human skin to doses of UV irradiation that induced mild sunburn resulted in the rapid appearance of ***p53*** protein in the epidermis and superficial dermal fibroblasts. Immunohistological analysis with a panel of antibodies established that while ***p53*** staining was not seen in normal skin it appeared within 2 h of UV exposure. The level of ***p53*** immunostaining peaked at 24 h and returned to undetectable levels within 360 h. The induction of proliferating cell nuclear antigen (PCNA)(which is required for both DNA replication and repair) followed a similar spatial and temporal pattern to ***p53*** . The UV irradiation did not induce a mitotic response or the replication-associated antigens DNA polymerase alpha or Ki67. The accumulation of high levels of ***p53*** and PCNA
in response to UV doses to which many human populations are routinely exposed provides strong support for a model in which normal ***p53*** acts as part of the ***DNA*** ***damage*** response in vertebrate cells. Such a model is consistent with the profound ***tumor*** -suppressor function of the ***p53*** gene, the high rate of ***p53*** mutation in neoplasia and the exceptionally high ***tumor***
susceptibility of ***p53*** -deficient mice.

L11 ANSWER 50 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93179686 EMBASE
DOCUMENT NUMBER: 1993179686
TITLE: Oncogenes and ***tumor*** suppressor genes.
AUTHOR: Carbone D.P.
CORPORATE SOURCE: Lung Cancer Clinic, Parkland Memorial Hospital,Dallas, TX,
United States
SOURCE: Hospital Practice, (1993) 28/6 (145-161).
ISSN: 8750-2836 CODEN: HOPRBW
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Molecular oncologists are elucidating the genetic mechanisms by which cancer cells proliferate. Prominent examples among dominant oncogenes include members of the ras family, which are activated by point mutations that perpetuate transduction of growth signals. The best-studied ***tumor*** suppressor gene is ***p53*** , which appears to be involved in the repair of ***damaged*** ***DNA*** .

L11 ANSWER 51 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:239935 BIOSIS
DOCUMENT NUMBER: PREV199344113135
TITLE: Characterization of the Drosophila homologue of the ***p53*** anti-oncogene and its response to ***DNA*** ***damage*** .
AUTHOR(S): Dusenbery, Ruth L.; Yakes, F. Michael
CORPORATE SOURCE: Dep. Chem., Wayne State Univ., Detroit, MI 48202 USA
SOURCE: Journal of Cellular Biochemistry Supplement, (1993) Vol. 0,
No. 17 PART A, pp. 136.
Meeting Info.: Keystone Symposium on Transcription: Factors, Regulation and Differentiation Keystone, Colorado, USA January 17-24, 1993
ISSN: 0733-1959.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 52 OF 82 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:618373 HCAPLUS
DOCUMENT NUMBER: 119:218373
TITLE: Mechanisms of action of ***p53***
AUTHOR(S): Barak, Y.; Ginsberg, D.; Michael, D.; Ragimov, N.; Shaulian, E.; Yonish-Rouach, E.; Zauberman, A.; Aloni, Y.; Oren, M.
CORPORATE SOURCE: Dep. Chem. Immunol., Weizmann Inst. Sci., Rehovot, 76100, Israel
SOURCE: Int. Congr. Ser. - Excerpta Med. (***1993***), 1016(Pharmacology of Cell Differentiation), 129-45
CODEN: EXMDA4; ISSN: 0531-5131
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 53 refs. The ***p53*** gene now appears to be a key player in cancer. The growing interest in ***p53*** has led to a very rapid increase in the understanding of its biol. and biochem., and this rapid rate of progress is likely to continue at least within the near future. The main conclusions so far have been that ***p53*** is likely to act as a sequence-specific transcription factor, and that it may be involved in the regulation of cell cycle progression, differentiation and cell death, at least in transformed cells. All these conclusions need to be evaluated in the context of two seminal ***p53*** -related findings made in the course of the last year. One of these findings is that mice can undergo apparently normal development without any ***p53*** . Thus ***p53*** "knock-out" mice, generated through homologous recombination, did not display any measurable defects at birth and during the first weeks of post-natal development, even though many of them subsequently came down with early onset ***tumors*** . Therefore, even if ***p53*** plays a role in such central processes as cell proliferation, apoptosis and differentiation, it is clearly not absolutely essential for any of these processes in fully normal cells. It is conceivable that the products of other genes can carry out efficiently all of those processes, perhaps substituting for ***p53*** in its absence. The second central finding is that wt ***p53*** is probably involved in the maintenance of genomic stability. There are now data which support strongly the possibility that ***p53*** is required for the cell to respond properly to ***DNA*** ***damage*** . In the presence of active wild-type ***p53*** , exposure to ***DNA*** ***damaging*** agents results in a transient G1 growth arrest, during which the lesions are repaired before any ***damaged*** ***DNA*** can be replicated. When ***p53*** is defunct or absent, the cells continue uninterruptedly into S phase; the ***damaged*** ***DNA*** is then replicated and the resultant genomic aberrations are perpetuated. The two findings may in fact be related, and may predict that the contribution of ***p53*** to development or to any other normal process will become evident only after some sort of ***DNA*** ***damage*** has occurred. Whether or not this turns out to be the case, it is obvious that a full elucidation of the importance of ***p53*** will require a much better understanding of its biochem., and particularly a definitive identification of its mol. targets.

L11 ANSWER 53 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:188081 BIOSIS
DOCUMENT NUMBER: PREV199497201081
TITLE: The Xiphophorus fish: A model for molecular mechanisms of environmental carcinogenesis.
AUTHOR(S): Ahmed, Farid E.
CORPORATE SOURCE: Biol. Dep., Brookhaven Natl. Lab., Upton, NY 11973 USA
SOURCE: Journal of Environmental Science and Health Part C Environmental Carcinogenesis & Ecotoxicology Reviews, (1993) Vol. 11, No. 2, pp. 125-161.
ISSN: 1059-0501.
DOCUMENT TYPE: General Review
LANGUAGE: English

L11 ANSWER 54 OF 82 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:505371 HCAPLUS
DOCUMENT NUMBER: 121:105371
TITLE: ***Tumor*** suppressor genes and molecular chaperones
AUTHOR(S): Lane, D.P.; Midgley, C.; Hupp, T.
CORPORATE SOURCE: Dep. Biochem., Univ. Dundee, Dundee, UK
SOURCE: Mol. Chaperones, [R. Soc. Discuss. Meet.] (***1993***), Meeting Date 1992, 113-17. Editor(s): Ellis, R. John; Laskey, Ronald A.; Lorimer, George H. Chapman & Hall: London, UK.
CODEN: 60DTAE
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review and discussion with many refs. The two ***tumor*** suppressor genes that are most commonly inactivated in human cancer are the ***p53*** gene on chromosome 17 and the retinoblastoma (Rb) gene on chromosome 11. Recent studies of both gene products suggest that they are able to act as powerful neg. regulators of cell division. The Rb gene seems to exert this activity by phys. complexing to a variety of specific transcription factors and inactivating their function. The capacity of Rb protein to bind these factors is regulated by phosphorylation. The Rb protein can therefore be seen to act as a chaperone for these factors. The ***p53*** protein also may act in part by regulating transcription but may also interact directly with the DNA replication app. The growth suppressive function of ***p53*** is induced by ***DNA*** ***damage*** leading to an attractive model of ***p53*** as an essential checkpoint control. The ***p53*** protein interacts with members of the hsp70 chaperone family which the authors now show can regulate its function.

L11 ANSWER 55 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93029555 EMBASE
DOCUMENT NUMBER: 1993029555
TITLE: DNA methylation and mutation.
AUTHOR: Holliday R.; Grigg G.W.
CORPORATE SOURCE: CSIRO Lab. for Molecular Biology, Division of Biomolecular Engineering, P.O. Box 184,North Ryde, NSW 2113, Australia
SOURCE: Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis, (1993) 285/1 (61-67).
ISSN: 0027-5107 CODEN: MRFMEC
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
022 Human Genetics
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 5-Methylcytosine (5mC) in DNA is produced by post-synthetic modification of cytosine residues, and it occurs primarily in CpG doublets in the mammalian genome. 5mC is a mutable site, because it can undergo

spontaneous deamination to thymine. There is a repair mechanism which specifically recognises G .cntdot. T mispairs, and replaces thymine with cytosine. However, this repair is not fully efficient, because the 5mC .fwdarw. T transition mutation occurs about 10 times as frequently as other transitions. Such mutations are frequently seen in inherited diseases, and mutations in the ***p53*** gene in tumours are also very commonly in 5mCpG doublets. As well as mutations, there can also be heritable changes in DNA methylation, known as epimutations, which may be
of particular significance in somatic cells. Whereas the pattern of DNA methylation is very constant for any one cell type, the pattern becomes very variable in tumour cells. The breakdown of the normal controls of DNA
methylation in ***tumorigenesis*** can lead to increased gene expression or to gene silencing. ***DNA*** ***damage*** increases
not only mutation, but also heritable changes in methylation. At present, little is known about the ability of DNA repair to preserve the normal pattern of methylation in somatic cells.

L11 ANSWER 56 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93079646 EMBASE
DOCUMENT NUMBER: 1993079646
TITLE: ***Tumor*** -suppressor ***p53*** and the cell cycle.
AUTHOR: Perry M.E.; Levine A.J.
CORPORATE SOURCE: Department of Molecular Biology, Lewis Thomas Laboratory,
Princeton University,Princeton, NJ 08544, United States
SOURCE: Current Opinion in Genetics and Development, (1993) 3/1 (50-54).
ISSN: 0959-437X CODEN: COGDET
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English

L11 ANSWER 57 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:286873 BIOSIS
DOCUMENT NUMBER: PREV199345004998
TITLE: Transgenic mice expressing mutant alleles of ***p53*** show increased resistance to gamma-radiation.
AUTHOR(S): Lee, Jonathan M. (1); Bernstein, Alan
CORPORATE SOURCE: (1) Div. Molecular Dev. Biol., Samuel Lunenfeld Res. Inst.,
Mount Sinai Hospital, 600 University Ave., Toronto, ON M5G 1X5 Canada
SOURCE: Environmental and Molecular Mutagenesis, (1993) Vol. 21,
No. SUPPL. 22, pp. 39.
Meeting Info.: 24th Annual Scientific Meeting of the Environmental Mutagen Society Norfolk, Virginia, USA April 17-22, 1993
ISSN: 0893-6692.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 58 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93305577 EMBASE
DOCUMENT NUMBER: 1993305577
TITLE: Cell checkpoint and radiosensitivity [9].
AUTHOR: Mumane J.P.; Schwartz J.L.
CORPORATE SOURCE: Radiobiol./Environmental Health Lab., University of
California,San Francisco, CA 94143-0750, United States
SOURCE: Nature, (1993) 365/6441 (22).
ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 014 Radiology
029 Clinical Biochemistry
LANGUAGE: English

L11 ANSWER 59 OF 82 MEDLINE
ACCESSION NUMBER: 92310556 MEDLINE
DOCUMENT NUMBER: 92310556 PubMed ID: 1614522
TITLE: Cancer. ***p53*** , guardian of the genome.
COMMENT: Comment on: Nature. 1992 Jul 2;358(6381):80-3
Comment on: Nature. 1992 Jul 2;358(6381):83-6
Comment in: Nature. 1992 Oct 8;359(6395):486-7
AUTHOR: Lane D P
SOURCE: NATURE, ***(1992 Jul 2)*** 358 (6381) 15-6.
Journal code: NSC; 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
Commentary
News Announcement
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920807
Last Updated on STN: 19950206
Entered Medline: 19920730

L11 ANSWER 60 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:478645 BIOSIS
DOCUMENT NUMBER: BA94:110020
TITLE: WILD-TYPE ***P53*** IS A CELL CYCLE CHECKPOINT
DETERMINANT FOLLOWING IRRADIATION.
AUTHOR(S): KUERBITZ S J; PLUNKETT B S; WALSH W V; KASTAN M B
CORPORATE SOURCE: DEP. ONCOLOGY, JOHNS HOPKINS UNIVERSITY SCHOOL MEDICINE,
BALTIMORE, MD. 21205.
SOURCE: PROC NATL ACAD SCI U S A, (1992) 89 (16), 7491-7495.
CODEN: PNASA6. ISSN: 0027-8424.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Cell cycle checkpoints appear to contribute to an increase in cell survival and a decrease in abnormal heritable genetic changes following exposure to ***DNA*** ***damaging*** agents. Though several radiation-sensitive yeast mutants have been identified, little is known about the genes that control these responses in mammalian cells. Recent studies from our laboratory have demonstrated a close correlation between expression of wild-type ***p53*** genes in human hematopoietic cells and their ability to arrest in G1 phase after certain types of ***DNA*** ***damage*** . In the present study, this correlation was first generalized to nonhematopoietic mammalian cells as well. A cause and effect relationship between expression of wild-type ***p53*** and the G1 arrest that occurs after .gamma. irradiation was then established by demonstrating acquisition of the G1 arrest after .gamma. irradiation following transfection of wild-type ***p53*** genes into cells lacking endogenous ***p53*** genes and loss of the G1 arrest after irradiation following transfection of mutant ***p53*** genes into cells with wild-type endogenous ***p53*** genes. A defined role for ***p53***

(the most commonly mutated gene in human cancers) in a physiologic pathway
has, to our knowledge, not been reported previously. Furthermore, these experiments illustrate one way in which a mutant ***p53*** gene product can function in a "dominant negative" manner. Participation of ***p53*** in this pathway suggests a mechanism for the contribution of abnormalities in ***p53*** to ***tumorigenesis*** and genetic instability and provides a useful model for studies of the molecular mechanisms of ***p53*** involvement in controlling the cell cycle.

L11 ANSWER 61 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92309529 EMBASE
DOCUMENT NUMBER: 1992309529
TITLE: Molecular basis of lymphomagenesis.
AUTHOR: Magrath I.
CORPORATE SOURCE: Lymphoma Biology Section, Pediatric Branch, National Cancer
Institute,Bethesda, MD 20892, United States
SOURCE: Cancer Research, (1992) 52/19 SUPPL. (5529s-5540s).
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy

006 Internal Medicine
016 Cancer
022 Human Genetics
025 Hematology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Lymphoid neoplasms, like all malignant ***tumors*** , arise as a consequence of the accumulation, in a single cell, of a set of genetic lesions that result in altered proliferation or increased clonal life span. The most frequently observed genetic abnormalities among the malignant non-Hodgkin's lymphomas are translocations, which appear to be lineage and, to a large extent, lymphoma specific. Recombinases that normally mediate the process of antigen receptor gene rearrangement appear to have an important (but not exclusive) role in the mediation of these translocations and of other types of gene fusion (e.g., deletion of intervening DNA). Frequently, such fusions result in the increased or inappropriate expression of crucially important proteins, many of which are transcription factors that regulate the expression of other genes. These abnormalities, however, do not appear to be sufficient to induce lymphoma, and it is likely that the additional genetic lesions required differ from one ***tumor*** to another. The likelihood of any given clone of cells accumulating a sufficient number of relevant genetic lesions to give rise to a lymphoma is probably a function of its life span. Prolonged survival of a cell clone may be mediated by viral genomes (e.g., Epstein-Barr virus and human T-cell leukemia/lymphoma virus type 1), by the abnormal expression of cellular genes that inhibit apoptosis (e.g., bcl-2), or by the mutation or deletion of cellular genes that are necessary for apoptosis, e.g., ***p53*** . The background rate at which genetic lesions occur is amplified by the interaction of inherited and environmental factors, the latter appearing to be the major determinant of incidence rates. However, inherited factors that influence lymphomagenesis, including variability in the ability to repair ***DNA*** ***damage*** or in the fidelity of antigen receptor recombinases for their signal sequences, may be crucial determinants of which particular individuals in a given environmental setting develop lymphoma.

L11 ANSWER 62 OF 82 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:631200 HCAPLUS
DOCUMENT NUMBER: 117:231200
TITLE: Molecular basis of lymphomagenesis
AUTHOR(S): Magrath, Ian
CORPORATE SOURCE: Pediatr. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Cancer Res. (***1992***), 52(19, Suppl.), 5529s-5540s
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 73 refs. Lymphoid neoplasms, like all malignant ***tumors*** , arise as a consequence of the accumulation, in a single cell, of a set of genetic lesions that result in altered proliferation or increased clonal life span. The most frequently obsd. genetic abnormalities among the malignant non-Hodgkin's lymphomas are translocations, which appear to be lineage and, to a large extent, lymphoma specific. Recombinases that normally mediate the process of antigen receptor gene rearrangement appear to have an important (but not exclusive) role in the mediation of these translocations and of other types of gene fusion (e.g., deletion of intervening DNA). Frequently, such fusions result in the increased or inappropriate expression of crucially important proteins, many of which are transcription factors that regulate the expression of other genes. These abnormalities, however, do not appear to be sufficient to induce lymphoma, and it is likely that the addnl. genetic lesions required differ from one ***tumor*** to another. The likelihood of any given clone of cells accumulating a sufficient no. of relevant genetic lesions to give rise to a lymphoma is probably a function of its life span. Prolonged survival of a cell clone may be mediated by viral genomes (e.g., Epstein-Barr virus and human T-cell leukemia/lymphoma virus type 1), by the abnormal expression of cellular genes that inhibit apoptosis (e.g., bcl-2), or by the mutation or deletion of cellular genes that are necessary for apoptosis, e.g., ***p53*** . The background rate at which genetic lesions occur is amplified by the interaction of inherited and environmental factors, the latter appearing to be the major determinant of incidence rates. However, inherited factors that influence lymphomagenesis, including variability in the ability to repair ***DNA*** ***damage*** or in the fidelity of antigen receptor recombinases for their signal sequences, may be crucial determinants of which particular individuals in a given environmental setting develop lymphoma.

L11 ANSWER 63 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93004612 EMBASE
DOCUMENT NUMBER: 1993004612
TITLE: Researchers gain insight into cell cycle delay.
AUTHOR: Bowersox J.
SOURCE: Journal of the National Cancer Institute, (1992) 84/24 (1859-1860).
ISSN: 0027-8874 CODEN: JNCIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English

L11 ANSWER 64 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:94833 BIOSIS
DOCUMENT NUMBER: PREV199395050029
TITLE: A mammalian cell cycle checkpoint pathway utilizing ***p53*** and GADD45 is defective in ataxia-telangiectasia.
AUTHOR(S): Kastan, Michael B. (1); Zhan, Qimin; El-Deiry, Wafik S. (1); Carrier, France; Jacks, Tyler; Walsh, William V. (1); Plunkett, Beverly S. (1); Vogelstein, Bert (1); Fornace, Albert J., Jr.
CORPORATE SOURCE: (1) Johns Hopkins Oncol. Cent., 600 North Wolfe St., Baltimore, Md. 21287
SOURCE: Cell, (1992) Vol. 71, No. 4, pp. 587-597.
ISSN: 0092-8674.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Cell cycle checkpoints can enhance cell survival and limit mutagenic events following ***DNA*** ***damage*** . Primary murine fibroblasts became deficient in a G1 checkpoint activated by ionizing radiation (IR) when both wild-type ***p53*** alleles were disrupted. In addition, cells from patients with the radiosensitive, cancer-prone disease ataxia-telangiectasia (AT) lacked the IR-induced increase in ***p53*** protein levels seen in normal cells. Finally, IR induction of the human GADD45 gene, an induction that is also defective in AT cells, was dependent on wild-type ***p53*** function. Wild-type but not mutant ***p53*** bound strongly to a conserved element in the GADD45 gene, and a ***p53*** -containing nuclear factor, which bound this element, was detected in extracts from irradiated cells. Thus, we identified three participants (AT gene(s), ***p53*** , and GADD45) in a signal transduction pathway that controls cell cycle arrest following ***DNA*** ***damage*** ; abnormalities in this pathway probably contribute to ***tumor*** development.

L11 ANSWER 65 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:59430 BIOSIS
DOCUMENT NUMBER: PREV199344025080
TITLE: Tumour suppression: Worrying about ***p53*** .
AUTHOR(S): Lane, David P.
CORPORATE SOURCE: Cancer Res. Lab., Univ. Dundee, Dundee DD1 4HN UK
SOURCE: Current Biology, (1992) Vol. 2, No. 11, pp. 581-583.
ISSN: 0960-9822.
DOCUMENT TYPE: Article
LANGUAGE: English

L11 ANSWER 66 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92315287 EMBASE
DOCUMENT NUMBER: 1992315287
TITLE: Checkpoint policing by ***p53*** [6].
AUTHOR: Carr A.M.; Green M.H.L.; Lehmann A.R.; Lane D.P.
CORPORATE SOURCE: MRC Cell Mutation Unit, Sussex University,Falmer BN1 9RR, United Kingdom
SOURCE: Nature, (1992) 359/6395 (486-487).

ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English

L11 ANSWER 67 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:438360 BIOSIS
DOCUMENT NUMBER: PREV199497451360
TITLE: Endogenously formed N-nitroso compounds and nitrosating agents in human cancer etiology.
AUTHOR(S): Bartsch, H. (1); Ohshima, H.; Pignatelli, B.; Calmels, S.
CORPORATE SOURCE: (1) Unit Environ. Carcinogens Host Factors, Internatl.
Agency Res. Cancer, Lyon France
SOURCE: Pharmacogenetics, (1992) Vol. 2, No. 6, pp. 272-277.
ISSN: 0960-314X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Humans are exposed to preformed N-nitroso compounds (NOC) dbldag , but
also to a wide range of precursors and nitrosating agents which can react in vivo to form potentially carcinogenic NOC and diazo compounds. Nitrite,
nitrate and nitrosating agents can also be synthesized endogenously in enzymic reactions mediated by bacteria, activated macrophages and neutrophils. The latter two cell types generate, via the enzyme nitric oxide synthase, the nitric oxide radical that is involved in cytotoxicity, and is believed to be involved in formation of carcinogenic nitrosamines, DNA base deamination and oxidative damage. Thus endogenous NOC formation,
DNA ***damage*** and gene mutations in humans could occur at
various sites of the body such as the stomach and chronically infected or inflamed organs. Sensitive procedures to estimate the exposure of humans to NOC have been developed and applied in ecological and cross-sectional
studies. These have shown that inhabitants of high-risk areas for stomach and esophageal cancer, patients with urinary tract infections (at risk for bladder cancer) and Thai subjects infected with liver fluke (at risk for cholangiocarcinoma) had significantly higher exposure to endogenous NOC.
Clinical studies have examined the model of stomach carcinogenesis based on intragastric nitrosation, but the precise roles of bacterial overgrowth and of Helicobacter pylori infection in NOC synthesis and/or inducing oxidative stress in stomach mucosa remain to be clarified. Together these results support the role of NOC and other nitrite-derived mutagens in human cancer etiology, in particular when exposure starts early in life and persists over a long period. In various human turnouts, C to T transition mutations have been frequently detected in the tumour-suppressor gene ***p53*** . Whether this type of mutation is mediated by nitric oxide synthase (via deamination of 5-methylcytosine to T at CpG islands) is now being examined in molecular pathology and epidemiological studies.

L11 ANSWER 68 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:364374 BIOSIS
DOCUMENT NUMBER: BR43:42524
TITLE: ***P53*** MUTATIONS AND AFLATOXIN EXPOSURE IN
HEPATOCELLULAR CARCINOMA.
AUTHOR(S): HOLLSTEIN M; WILD C P; BENNETT W; BLEICHER F; CHUTIMATAEWIN
S; HARRIS C C; SRIVATANAKUL P; YU S; MONTESANO R
CORPORATE SOURCE: IARC, LYON, FRANCE.
SOURCE: 83RD ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER
RESEARCH, SAN DIEGO, CALIFORNIA, USA, MAY 20-23, 1992. PROC
AM ASSOC CANCER RES ANNU MEET, (1992) 33 (0), 172.
CODEN: PAMREA.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L11 ANSWER 69 OF 82 MEDLINE
ACCESSION NUMBER: 93137815 MEDLINE
DOCUMENT NUMBER: 93137815 PubMed ID: 1486846
TITLE: Molecular epidemiology in cancer risk assessment and prevention: recent progress and avenues for future research.
AUTHOR: Wogan G N
CORPORATE SOURCE: Department of Chemistry, Massachusetts Institute of
Technology, Cambridge 02139.
SOURCE: ENVIRONMENTAL HEALTH PERSPECTIVES, ***(1992 Nov)*** 98
167-78. Ref: 82
Journal code: EI0; 0330411. ISSN: 0091-6765.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199302
ENTRY DATE: Entered STN: 19930312
Last Updated on STN: 19930312
Entered Medline: 19930224
AB Molecular epidemiology is increasingly being applied in studies of cancer
risks derived from exposure to environmental carcinogens of both endogenous and exogenous origins. Analytical methods have been developed
that are capable of detecting and quantifying levels of covalent adducts of several important classes of carcinogens with cellular DNA and blood proteins. Methods of sufficient sensitivity and specificity to detect ambient levels of exposure are in current use. These are being used in studies related to tobacco use (polycyclic aromatic hydrocarbons, aromatic amines, tobacco-specific nitrosamines); dietary exposures (aflatoxins, N-nitrosamines, heterocyclic amines); medicinal exposures (cisplatin, alkylating agents, 8-methoxypsoralen, ultraviolet photoproducts); occupational exposures (aromatic amines, polycyclic aromatic hydrocarbons,
oxides of ethylene and styrene, and vinyl chloride); and oxidative damage (8-hydroxyguanine, thymine glycol). Methodologic improvements together with their expanded use in feasibility studies continue to produce results that support the validity of this approach for detecting and quantifying exposure to carcinogens. Genetic markers are also being used to detect early biological responses in efforts to link carcinogen exposure to initiating events in the carcinogenesis process. These include, in addition to traditional cytogenetic markers (e.g., chromosomal aberrations, sister chromatid exchange, micronuclei), other alterations in chromosomal structure such as restriction fragment length polymorphisms, loss of heterozygosity, and translocation markers. Specific genetic changes have recently been identified as critical molecular events in the initiation and development of many cancers. Important among these are activation of oncogenes, especially those of the ras family, and inactivation of ***tumor*** -suppressor genes (e.g., ***p53*** and Rb) by point mutations and/or chromosomal deletions and other structural changes. Although some of these changes are known to occur in chemically
induced ***tumors*** of experimental animals, the possible role of chemical carcinogens in the induction of genetic abnormalities in human cancers has yet to be determined. Continuing investigations employing the methods of molecular epidemiology promise to provide further evidence concerning these relationships. Future investigations employing newly developed molecular biological methods, in particular those based on polymerase chain reaction amplification of DNA, to identify alterations in DNA and chromosomal structure, combined with methods for characterizing
exposure to carcinogens and early effects, have great potential for further elucidating the role of genotoxic agents in the etiology of human cancers and also for the development of strategies for their prevention.

L11 ANSWER 70 OF 82 MEDLINE
ACCESSION NUMBER: 93145018 MEDLINE
DOCUMENT NUMBER: 93145018 PubMed ID: 1362682
TITLE: The pathogenesis of AIDS lymphomas: a foundation for addressing the challenges of therapy and prevention.
AUTHOR: Karp J E; Broder S
CORPORATE SOURCE: Office of the Director, National Cancer Institute, Bethesda, Maryland 20892.
SOURCE: LEUKEMIA AND LYMPHOMA, ***(1992 Oct)*** 8 (3) 167-88.

Ref: 145
Journal code: BNQ; 9007422. ISSN: 1042-8194.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199302
ENTRY DATE: Entered STN: 19930312
Last Updated on STN: 19980206
Entered Medline: 19930226

AB The association between AIDS and a spectrum of malignancies relates to chronic, profound defects in both cellular and humoral mechanisms of immune surveillance. Ironically, as AIDS patients live longer in response to increasingly effective antiretroviral therapies, the incidence of AIDS-related malignancies will continue to rise. The emergence of non-Hodgkin's lymphomas (NHL) as a major sequela of HIV infection bears a striking relationship to depletion of CD4 lymphocytes, particularly below 50/mm3. The ability to interfere early in the course of active HIV infection with additional mechanisms that may promulgate transformed cell hyperproliferation and clonal expansion--growth factors, HIV itself or other viruses (Epstein-Barr, in particular), aberrant oncogene or ***tumor*** suppressor genes expression, factors that induce genetic instability or ***DNA*** ***damage*** or alter host or viral genome repair--might decrease the occurrence or prolong the time to development of AIDS-related malignancies. The development of antiretroviral strategies that confer long-term suppression of HIV activity and relative preservation of immune function are essential to the ultimate prevention of malignancies that arise as a consequence of HIV-induced immunosuppression.

L11 ANSWER 71 OF 82 MEDLINE
ACCESSION NUMBER: 92323544 MEDLINE
DOCUMENT NUMBER: 92323544 PubMed ID: 1623518
TITLE: Ras-induced hyperplasia occurs with mutation of ***p53***
, but activated ras and myc together can induce carcinoma without ***p53*** mutation.
AUTHOR: Lu X; Park S H; Thompson T C; Lane D P
CORPORATE SOURCE: Department of Biochemistry, University of Dundee, Scotland.
CONTRACT NUMBER: CA-50588 (NCI)
DK-43523 (NIDDK)
SOURCE: CELL, ***(1992 Jul 10)*** 70 (1) 153-61.
Journal code: CQ4; 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920821
Last Updated on STN: 19970203
Entered Medline: 19920811

AB Using a reconstituted mouse prostate organ, the effects on endogenous ***p53*** expression of the ras oncogene or of the ras + myc oncogenes were investigated. In this system the ras gene alone causes mild hyperplasia, but the combination of ras and myc leads to the formation of carcinomas. Surprisingly, while ***p53*** mutations were found in cells derived from the reconstituted organs containing ras alone, no such mutations were found in the ras + myc-transformed cells. Their growth, unlike that of the cells containing ras alone, was not inhibited by transfection with plasmids encoding wild-type human ***p53*** . We suggest that expression of both activated ras and myc genes bypasses the need for ***p53*** mutation by neutralizing the ***tumor*** suppressor activity of normal ***p53*** .

L11 ANSWER 72 OF 82 MEDLINE
ACCESSION NUMBER: 92409653 MEDLINE
DOCUMENT NUMBER: 92409653 PubMed ID: 1528930
TITLE: Molecular alterations in human skin ***tumors*** .
AUTHOR: Ananthaswamy H N; Pierceall W E
CORPORATE SOURCE: Department of Immunology, University of Texas M. D. Anderson Cancer Center, Houston 77030.
CONTRACT NUMBER: R01-CA-46523 (NCI)
T32-CA-09598 (NCI)
SOURCE: PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH, ***(1992)*** 376 61-84. Ref: 131
Journal code: PZ5; 7605701. ISSN: 0361-7742.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199210
ENTRY DATE: Entered STN: 19921106
Last Updated on STN: 19921106
Entered Medline: 19921022

AB Several genetic alterations that perturb normal cellular growth control mechanisms can cause cancers. These include point mutations, deletions, translocations, amplifications and gene rearrangements and occur primarily in two classes of interacting genes, oncogenes and ***tumor*** suppressor genes. While mutation or amplification of certain oncogenes can facilitate cell growth and ***tumor*** formation (Bishop, 1983, 1991; Hunter, 1991; Land, et al., 1983), loss or mutation of ***tumor*** suppressor genes, which normally inhibit these processes, can promote ***tumor*** formation (Knudson, 1985; Cavenee, et al., 1989; Marshall, 1991). Human skin ***tumors*** display multiple genetic alterations such as Ha-ras gene mutation and LOH, N-ras gene amplification, and mutations in ***p53*** ***tumor*** suppressor gene. In most cases, the mutations in ras and ***p53*** genes are localized to pyrimidine-rich sequences, particularly C-C sequences, which indicates that these sites are probably the targets for UV-induced ***DNA*** ***damage*** and subsequent mutation and transformation. Since UV radiation in sunlight is an environmental carcinogen it is important to understand the molecular mechanisms by which UV radiation induces human skin cancers. In addition, suitable animals models are available for comparative studies and risk assessment. By comparing the various genetic alterations detected in sunlight-induced human skin ***tumors*** with those present in UV-induced murine skin ***tumors*** , it may be possible to identify the carcinogen-related events that are involved in the multi-step process of carcinogenesis. Studies addressing these issues should provide further insights into the molecular mechanisms of UV carcinogenesis.

L11 ANSWER 73 OF 82 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92204366 EMBASE
DOCUMENT NUMBER: 1992204366
TITLE: ***p53*** , guardian of the genome.
AUTHOR: Lane D.P.
CORPORATE SOURCE: Cancer Research Campaign Labs., University of Dundee,Dundee
DD1 4HN, United Kingdom
SOURCE: Nature, (1992) 358/6381 (15-16).
ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 016 Cancer
022 Human Genetics
LANGUAGE: English

L11 ANSWER 74 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:62817 BIOSIS
DOCUMENT NUMBER: PREV199344028467
TITLE: ***P53*** ***Tumor*** suppressor product in rat lung alveolar macrophages after asbestos exposure in vivo.
AUTHOR(S): Wiethege, T.; Kerenyi, T.; Voss, B.; Mueller, K. M.
CORPORATE SOURCE: Professional Associations Res. Inst. Occupational Med., Ruhr Univ., Bochum Germany
SOURCE: Journal of Leukocyte Biology, (1992) Vol. 0, No. SUPPL. 3, pp. 13.

Meeting Info.: Twenty-ninth National Meeting of the Society for Leukocyte Biology, Charleston, South Carolina, USA, December 2-5, 1992. J LEUKOCYTE BIOL
ISSN: 0741-5400.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 75 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:74020 BIOSIS
DOCUMENT NUMBER: BA93:42475
TITLE: PARTICIPATION OF ***P53*** PROTEIN IN THE CELLULAR
RESPONSE TO ***DNA*** ***DAMAGE*** .
AUTHOR(S): KASTAN M B; ONYEKWERE O; SIDRANSKY D; VOGELSTEIN B; CRAIG R
W
CORPORATE SOURCE: ONCOL. 3-120, JOHNS HOPKINS HOSP., 600 NORTH WOLFE ST.,
BALTIMORE, MD. 21205.
SOURCE: CANCER RES, (1991) 51 (23 PART 1), 6304-6311.
CODEN: CNREA8. ISSN: 0008-5472.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The inhibition of replicative DNA synthesis that follows ***DNA*** ***damage*** may be critical for avoiding genetic lesions that could contribute to cellular transformation. Exposure of ML-1 myeloblastic leukemia cells to nonlethal doses of the ***DNA*** ***damaging*** agents, .gamma.-irradiation or actinomycin D, causes a transient inhibition of replicative DNA synthesis via both G1 and G2 arrests. Levels of ***p53*** protein in ML-1 cells and in proliferating normal bone marrow myeloid progenitor cells increase and decrease in temporal association with the G1 arrest. In contrast, the S-phase arrest of ML-1 cells caused by exposure to the anti-metabolite, cytosine arabinoside, which does not directly ***damage*** ***DNA*** , is not associated with a significant change in ***p53*** protein levels. Caffeine treatment blocks both the G1 arrest and the induction of ***p53*** protein after .gamma.-irradiation, thus suggesting that blocking the induction of ***p53*** protein may contribute to the previously observed effects of caffeine on cell cycle changes after ***DNA*** ***damage*** . Unlike ML-1 cells and normal bone marrow myeloid progenitor cells, hematopoietic cells that either lack ***p53*** gene expression or overexpress a mutant form of the ***p53*** gene do not exhibit a G1 arrest after .gamma.-irradiation; however, the G2 arrest is unaffected by the status of the ***p53*** gene. These results suggest a role for the wild-type ***p53*** protein in the inhibition of DNA synthesis that follows ***DNA*** ***damage*** and thus suggest a new mechanism for how the loss of wild-type ***p53*** might contribute
to ***tumorigenesis*** .

L11 ANSWER 76 OF 82 MEDLINE
ACCESSION NUMBER: 91356525 MEDLINE
DOCUMENT NUMBER: 91356525 PubMed ID: 1884379
TITLE: Chemical and physical carcinogenesis: advances and perspectives for the 1990s.
AUTHOR: Harris C C
CORPORATE SOURCE: Laboratory of Human Carcinogenesis, National Cancer
Institute, NIH, Bethesda, Maryland 20892.
SOURCE: CANCER RESEARCH, ***(1991 Sep 15)*** 51 (18 Suppl)
5023s-5044s. Ref: 468
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911027
Last Updated on STN: 19911027
Entered Medline: 19911004
AB Carcinogenesis is a multistage process driven by carcinogen-induced genetic and epigenetic damage in susceptible cells that gain a selective growth advantage and undergo clonal expansion as the result of activation of protooncogenes and/or inactivation of ***tumor*** suppressor genes.
Therefore, the mutational spectra of chemical and physical carcinogens in these critical genes are of interest to define endogenous and exogenous mutational mechanisms. The ***p53*** ***tumor*** suppressor gene
is ideally suited for analysis of the mutational spectrum. Such an analysis has revealed evidence for both exogenous and endogenous molecular
mechanisms of carcinogenesis. For example, an informative ***p53*** mutational spectrum of frequent G----T transversions in codon 249 is found
in hepatocellular carcinomas from either Qidong, People's Republic of China, or southern Africa. This observation links exposure to aflatoxin B1, a known cancer risk factor in these geographic regions, with a specific mutation in a cancer-related gene. Other studies indicate that abnormalities in genes controlling the cell cycle may cause genomic instability and increase the probability of neoplastic transformation. Finally, mechanistic understanding of carcinogenesis is leading to improved cancer risk assessment and to the identification of individuals at high cancer risk.

L11 ANSWER 77 OF 82 MEDLINE
ACCESSION NUMBER: 91309098 MEDLINE
DOCUMENT NUMBER: 91309098 PubMed ID: 1855226
TITLE: Genetic analysis of human esophageal ***tumors*** from two high incidence geographic areas: frequent ***p53*** base substitutions and absence of ras mutations.
AUTHOR: Hollstein M C; Peri L; Mandard A M; Welsh J A; Montesano R;
Metcalf R A; Bak M; Harris C C
CORPORATE SOURCE: Laboratory of Human Carcinogenesis, National Cancer
Institute, NIH, Bethesda, Maryland 20892.
SOURCE: CANCER RESEARCH, ***(1991 Aug 1)*** 51 (15) 4102-6.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910913
Last Updated on STN: 19910913
Entered Medline: 19910828
AB Esophageal squamous cell carcinoma (ESC) samples from patients residing in
Uruguay and in Normandy, France, where alcoholic beverages and tobacco
smoke are major risk factors, were analyzed for point mutations in the ***p53*** ***tumor*** suppressor gene. Among 34 ***tumors*** (15
from Normandy and 19 from Uruguay) 15 point mutations in the ***p53***
gene that result in amino acid substitutions or chain termination were identified by polymerase chain reaction amplification of exons 5-8 and direct DNA sequencing. Base substitutions in ESC from these high-incidence
areas are dispersed over the midregion of the ***p53*** gene. There are differences between ESC and other types of gastrointestinal cancer in the nature of frequent base substitutions. CpG to TpG transitions were far less prevalent in these ESC than in colorectal ***tumors*** , whereas G to T transversions, rarely found in colon cancers, were found in one-fourth of the ESC samples. Base substitutions at A:T pairs constitute an important fraction of ESC ***p53*** mutations, in contrast to mutation patterns in most other types of solid ***tumors*** . In contrast to the frequent mutation of the ***p53*** gene in these samples, no mutations in the H-, K-, or N-ras genes were found in 16 ***tumors*** from Uruguay by direct sequencing of exons in which transforming mutations are known to occur. A previous study on ras mutations in ESC from France was also negative (M. C. Hollstein et al., Cancer Res., 48: 5119-5123, 1988). The role of distinct etiological factors in generating these differences and the potential for linking patient exposure histories with patterns of ***p53*** mutations in high risk populations are considered.

L11 ANSWER 78 OF 82 MEDLINE
ACCESSION NUMBER: 91369778 MEDLINE
DOCUMENT NUMBER: 91369778 PubMed ID: 1679993
TITLE: Genomic instability and cancer: cause and effect.

AUTHOR: Cheng K C; Diaz M O
CORPORATE SOURCE: Department of Pathology, University of Washington, Seattle
98195.
SOURCE: CANCER CELLS, ***(1991 May)*** 3 (5) 188-92.
Journal code: AU5; 9000382. ISSN: 1042-2196.
PUB. COUNTRY: United States
Conference; Conference Article; (CONGRESSES)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911108
Last Updated on STN: 19990129
Entered Medline: 19911018

L11 ANSWER 79 OF 82 MEDLINE
ACCESSION NUMBER: 92000375 MEDLINE
DOCUMENT NUMBER: 92000375 PubMed ID: 1910603
TITLE: Biochemical and molecular epidemiology of cancer.
AUTHOR: Sugimura H; Weston A; Caporaso N E; Shields P G; Bowman E
D; Metcalf R A; Harris C C
CORPORATE SOURCE: Laboratory of Human Carcinogenesis, National Cancer
Institute, National Institutes of Health, Rockville, Maryland 20892.
SOURCE: BIOMEDICAL AND ENVIRONMENTAL SCIENCES, ***(1991 Jun)***
4 (1-2) 73-92. Ref: 159
Journal code: AHX; 8909524. ISSN: 0895-3988.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199111
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 19920124
Entered Medline: 19911121
AB Examples of practical approaches to molecular epidemiology of human cancer
are described. Biomarkers of carcinogen exposure or inherited host factors for cancer susceptibility are discussed. Major advances have been made in the detection of carcinogenmacromolecular adducts through the use of high
performance liquid chromatography, immunoaffinity chromatography, the 32P-postlabeling assay, enzyme immunoassays, gas chromatography/mass spectroscopy and synchronous spectrophotofluorimetry. The polycyclic aromatic hydrocarbon-DNA adducts are the most extensively studied in this
field and together with antibodies to these adducts found in human serum, they have become useful indicators of exposure to carcinogens. Assays for various kinds of alkyl-DNA adducts have also been developed and the presence of these adducts have been documented in human tissues. Carcinogen-protein adducts have proven to be useful molecular dosimeters of carcinogen exposure. For example, 4-aminobiphenyl hemoglobin adducts
are highly correlated with exposure to tobacco smoke. The study of the molecular aspects of interindividual differences in the metabolism and activation of xenobiotics and other genetic markers [DNA-restriction fragment length polymorphisms (RFLPs), mutations, and functional loss of specific genes in carcinogenesis] is an emerging new field that is discussed in the context of genetic susceptibility to cancer. The cytochrome P450 phenotypes and acetylation phenotype are examples of genetic markers that indicate an individual's potential for metabolism of exogenous substances. Further, inherited genetic polymorphic markers, e.g., DNA-RFLPs at protooncogene loci (HRAS-1 and L-myc) have been examined in a case-control study of lung cancer. Data concerning mutations
of protooncogenes (H-, K-, and N-RAS) and ***tumor*** suppressor genes
(retinoblastoma and ***p53*** genes) in various common cancers are providing evidence of multiple genetic lesions that occur during the multistage process of carcinogenesis.

L11 ANSWER 80 OF 82 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1991:147951 BIOSIS
DOCUMENT NUMBER: BR40:67556
TITLE: ONCOGENES IN HUMAN LUNG CANCER.
AUTHOR(S): KAYE F J; BARKSDALE S K; HARBOUR J W; MINNA J D
CORPORATE SOURCE: NCI-NAVY MED. ONCOL. BRANCH, NATL. CANCER INST. AND NAVAL
HOSP., BETHESDA, MD. 20814, USA.
SOURCE: SLUYSER, M. (ED.). ELLIS HORWOOD SERIES IN MOLECULAR
BIOLOGY: MOLECULAR BIOLOGY OF CANCER GENES. 292P. ELLIS
HORWOOD LTD.: CHICHESTER, ENGLAND, UK; NEW YORK, NEW YORK,
USA. ILLUS, (1990) 0 (0), 207-222.
ISBN: 0-13-599614-7.
FILE SEGMENT: BR; OLD
LANGUAGE: English

L11 ANSWER 81 OF 82 MEDLINE
ACCESSION NUMBER: 90297884 MEDLINE
DOCUMENT NUMBER: 90297884 PubMed ID: 2193649
TITLE: Cellular and molecular biological aspects of human bronchogenic carcinogenesis.
AUTHOR: Willey J C; Harris C C
CORPORATE SOURCE: Division of Cancer Etiology, National Cancer Institute,
National Institutes of Health, Bethesda, Maryland.
SOURCE: CRITICAL REVIEWS IN ONCOLOGY/HEMATOLOGY, ***(1990)***
10 (2) 181-209. Ref: 244
Journal code: AGO; 8916049. ISSN: 1040-8428.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900907
Last Updated on STN: 19900907
Entered Medline: 19900808
AB This is a time of rapid progress in the field of human bronchogenic carcinogenesis due to recent advances in cellular and molecular biology. Important developments over the last 10 years include establishment of methods for culturing NHBE cells under defined conditions, and molecular biological and biochemical epidemiological techniques for identifying genetic changes that are associated with malignant transformation of these cells. Most progress in defining genes associated with human carcinogenesis has been due to discoveries related to oncogenes and more recently, ***tumor*** suppressor genes. As was described in Section II.B.3.a, we now know that oncogene products serve as growth factors, growth factor receptors, and cytosolic and nuclear regulatory proteins. In addition, although the actions of putative ***tumor*** suppressor genes are less well understood, the first isolated ***tumor*** suppressor gene Rb, interacts with the products of DNA viruses which, in turn, are involved in regulation of transcription as was described in Section II.B.3.b. Thus, not surprisingly, both oncogenes and ***tumor***
suppressor genes code for classes of proteins that are known to play an important role in regulation of cell proliferation. Recently, a second gene that appears to possess ***tumor*** suppression activity (***p53***) has been identified on the short arm of chromosome 17 (17p).
The initial data suggesting a possible ***tumor*** suppressor gene on chromosome 17p came from cytogenetic and RFLP studies associating loss of
heterozygosity in the chromosome 17p13 region with ***tumor*** cells and tissues. Since the ***p53*** gene is located in this region it was evaluated and found to be frequently or always altered in several types of ***tumor*** cells. Recently, it was determined that introduction of the wild-type ***p53*** gene into NIH3T3 cells will inhibit subsequent malignant transformation. Thus, the preponderance of evidence now supports
the hypothesis that while mutated ***p53*** acts as an oncogene, the wild-type ***p53*** gene codes for a ***tumor*** suppressor function. The role of balance between oncogenes and ***tumor*** suppressor genes in control of proliferation is presently an active area of investigation. As discussed, introduction of a chromosome containing a

tumor suppressor gene will suppress ***tumorigenicity*** of a malignant cell line, even though that cell line possesses an active c-Ha-ras oncogene. Whether or not the level of expression of an activated oncogene is related to ***tumorigenicity*** is presently being investigated.(ABSTRACT TRUNCATED AT 400 WORDS)

L11 ANSWER 82 OF 82 MEDLINE
ACCESSION NUMBER: 90262567 MEDLINE
DOCUMENT NUMBER: 90262567 PubMed ID: 2140509
TITLE: ***Tumor*** suppressor genes.
AUTHOR: Levine A J
CORPORATE SOURCE: Department of Biology, Lewis Thomas Laboratory, Princeton
University, New Jersey 08544-1014.
CONTRACT NUMBER: P01-CA41086-04 (NCI)
SOURCE: BIOESSAYS, ***(1990 Feb)*** 12 (2) 60-6. Ref: 21
Journal code: 9YY; 8510851. ISSN: 0265-9247.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199006
ENTRY DATE: Entered STN: 19900720
Last Updated on STN: 19900720
Entered Medline: 19900627

AB The retinoblastoma sensitivity protein (Rb) and the ***p53*** gene product both appear to function as negative regulators of cell division or abnormal cellular growth in some differentiated cell types. Several types of cancers have been shown to be derived from cells that have extensively mutated both alleles of one or both of these genes, resulting in a loss-of-function mutation. In the case of the ***p53*** gene, this mutational process appears to occur in two steps, with the first mutation at the ***p53*** locus resulting in a trans-dominant phenotype. The mutant ***p53*** gene product enters into an oligomeric protein complex with the wild-type ***p53*** protein derived from the other normal allele and such a complex is inactive or less efficient in its negative regulation of growth control. This intermediate stage of carcinogenesis selects for the proliferation of cells with one mutant allele, enhancing the probability of obtaining a cancer cell with both alleles ***damaged*** . The ***DNA*** ***tumor*** viruses have evolved mechanisms to interact with the Rb and ***p53*** negative regulators of cellular growth in order to enhance their own replication in growing cells. SV40 and adenovirus type 5 produce viral encoded proteins that also form oligomeric protein complexes with ***p53*** and Rb, presumably inactivating their functions. These viral proteins are also the oncogene products of these viruses. Thus, the mechanisms by which cancer may arise in a host, via mutations or virus infections, have fundamental common pathways effecting the same cellular genes and gene products; Rb and ***p53*** .

=> s p53
L1 99060 P53

=> s tumor or cancer
L2 2856946 TUMOR OR CANCER

=> s express or expressed or expression or expressing or expresses
L3 2999137 EXPRESS OR EXPRESSED OR EXPRESSION OR EXPRESSING OR EXPRESSES

=> s dna damag?
L4 89149 DNA DAMAG?

=> s l1 and l2 and l3
L5 38493 L1 AND L2 AND L3

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L6 8343056 INHIBIT OR INHIBITS OR INHIBITION OR INHIBITED OR REDUCE OR
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L7 3603 L1 AND L2 AND L3 AND L4

=> s l1 and l2 and l3 and l4 and l6
L8 1415 L1 AND L2 AND L3 AND L4 AND L6

=> s l8 and py<1995
1 FILES SEARCHED...
3 FILES SEARCHED...
4 FILES SEARCHED...
L9 77 L8 AND PY<1995

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PROCESSING COMPLETED FOR L9
L10 36 DUP REM L9 (41 DUPLICATES REMOVED)

=> d l10 ibib abs 1-36

L10 ANSWER 1 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
ACCESSION NUMBER: 1995:77919 BIOSIS
DOCUMENT NUMBER: PREV199598092219
TITLE: Characterization of human Gadd45, a ***p53*** -regulated
protein.
AUTHOR(S): Carrier, France (1); Smith, Martin L.; Bae, Insoo; Kilpatrick, Katherine E.; Lansing, Timothy J.; Chen, Chaw-Yuan; Engelstein, Marcy; Friend, Steve H.; Henner, W. David; Gilmer, Tona M.; Kastan, Michael B.; Fornace, Albert J., Jr.
CORPORATE SOURCE: (1) Lab. Mol. Pharmacol., DTP, DCT, NCI, National Inst.
Health, Bethesda, MD 20892 USA
SOURCE: Journal of Biological Chemistry, (1994) Vol. 269, No. 51, pp. 32672-32677.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB GADD45 (growth arrest and ***DNA*** ***damage***) is a ***DNA***
- ***damage*** -inducible gene regulated in part by the ***tumor*** suppressor ***p53*** . A role in negative growth control has recently been suggested based on significant (more than 75%) ***reduction*** of
colony formation following over ***expression*** of Gadd45. To better
understand the role of Gadd45, we have developed specific rabbit and murine antibodies raised against the human recombinant protein. Using these antibodies, we have found that in ML-1 cells Gadd45 is predominantly
a nuclear protein. MyD118, a protein induced by terminal differentiation sharing 57% homology with Gadd45, does not cross-react with any of the antibodies produced. As expected, the induction of Gadd45 protein by ionizing radiation (IR) was also found to be dependent on a wild type ***p53*** phenotype. Interestingly, WI-L2-NS, a human lymphoid cell line, showed very high basal levels of Gadd45 mRNA and protein in addition
to a high constitutive level of a mutated ***p53*** protein. In this cell line, the high levels of GADD45 did not ***inhibit*** cellular growth in spite of the fact that no mutations were found in GADD45 sequence. These results indicate that some cell line(s) can tolerate high levels of Gadd45 and abrogate its growth suppression function.

L10 ANSWER 2 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:446709 BIOSIS
DOCUMENT NUMBER: PREV199497459709
TITLE: Hypoxia induces accumulation of ***p53*** protein, but activation of a G-1-phase checkpoint by low-oxygen conditions.
AUTHOR(S): Graeber, Thomas G.; Peterson, Joseph F.; Tsai, Mitchell; Monica, Katherine; Fornace., Albert J., Jr.; Giaccia, Amato J. (1)
CORPORATE SOURCE: (1) Dep. Radiation Oncol., Stanford Univ. Sch. Med.,
Stanford, CA 94305 USA
SOURCE: Molecular and Cellular Biology, (1994) Vol. 14, No. 9, pp.
6264-6277.
ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
AB It has been convincingly demonstrated that genotoxic stresses cause the accumulation of the ***tumor*** suppressor gene ***p53*** . One important consequence of increased ***p53*** protein levels in response to ***DNA*** ***damage*** is the activation of a G-1-phase cell cycle checkpoint. It has also been shown that G-1-phase cell cycle checkpoints are activated in response to other stresses, such as lack of oxygen. Here we show that hypoxia and heat, agents that induce cellular stress primarily by inhibiting oxygen-dependent metabolism and denaturing proteins, respectively, also cause an increase in ***p53*** protein levels. The ***p53*** protein induced by heat is localized in the cytoplasm and forms a complex with the heat shock protein hsc70. The increase in nuclear ***p53*** protein levels and DNA-binding activity and the induction of reporter gene constructs containing ***p53*** binding sites following hypoxia occur in cells that are wild type for ***p53*** but not in cells that possess mutant ***p53*** . However, unlike ionizing radiation, the accumulation of cells in G-1 phase by hypoxia is not strictly dependent on wild-type ***p53*** function. In addition, cells ***expressing*** the human papillomavirus E6 gene, which show increased degradation of ***p53*** by ubiquitination and fail to accumulate ***p53*** in response to ***DNA*** - ***damaging*** agents, do increase their ***p53*** levels following heat and hypoxia. These results suggest that hypoxia is an example of a "nongenotoxic" stress which induces ***p53*** activity by a different pathway than ***DNA*** - ***damaging*** agents.

L10 ANSWER 3 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
ACCESSION NUMBER: 1994:438337 BIOSIS
DOCUMENT NUMBER: PREV199497451337
TITLE: The ability of human papillomavirus E6 proteins to target ***p53*** for degradation in vivo correlates with their ability to abrogate actinomycin D-induced growth arrest.
AUTHOR(S): Foster, Scott A.; Demers, G. William; Etscheid, Beth G.; Galloway, Denise A. (1)
CORPORATE SOURCE: (1) Fred Hutchinson Cancer Res. Center, 1124 Columbia St.,
Seattle, WA 98104 USA
SOURCE: Journal of Virology, (1994) Vol. 68, No. 9, pp. 5698-5705.
ISSN: 0022-538X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Functional ***p53*** protein is associated with the ability of cells to arrest in G-1 after ***DNA*** ***damage*** . The E6 protein of ***cancer*** -associated human papillomavirus type 16 (HPV-16) binds to
p53 and targets its degradation through the ubiquitin pathway. To

determine whether the ability of E6 to interact with ***p53*** leads to a disruption of cell cycle control, mutated E6 proteins were tested for ***p53*** binding and ***p53*** degradation targeting in vitro, the ability to ***reduce*** intracellular ***p53*** levels in vivo, and the ability to abrogate actinomycin D-induced growth arrest in human keratinocytes. Mutations scattered throughout the amino terminus, either zinc finger or the central region but not the carboxy terminus, severely ***reduced*** the ability of E6 to interact with ***p53*** . ***Expression*** of HPV-16 E6 or mutated E6 proteins that bound and targeted ***p53*** for degradation in vitro sharply ***reduced*** the level of intracellular ***p53*** induced by actinomycin D in human keratinocytes. A perfect correlation between the ability of E6 proteins to ***reduce*** the level of intracellular ***p53*** and their ability to block actinomycin D-induced cellular growth arrest was observed. These results suggest that interaction with ***p53*** is important for the ability of HPV E6 proteins to circumvent growth arrest.

L10 ANSWER 4 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
ACCESSION NUMBER: 1994:347528 BIOSIS
DOCUMENT NUMBER: PREV199497360528
TITLE: ***P53*** -Dependent G-1 arrest involves pRB-related proteins and is disrupted by the human papillomavirus 16 E7 oncoprotein.
AUTHOR(S): Slebos, Robbert J. C.; Lee, Mann H.; Plunkett, Beverly S.; Kessis, Theodore D.; Williams, Bart O.; Jacks, Tyler; Hedrick, Lora; Kastan, Michael B.; Cho, Kathleen R. (1)
CORPORATE SOURCE: (1) Dep. Pathol., Johns Hopkins Univ. Sch. Med., Baltimore, MD 21205 USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1994) Vol. 91, No. 12, pp. 5320-5324.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The cell cycle regulatory ***tumor*** suppressor proteins ***p53*** and pRB are targeted for inactivation by several ***tumor*** viruses, including the high-risk types of human papillomaviruses (HPVs) via interactions of the HPV E6 and E7 oncoproteins with ***p53*** and pRB, respectively. ***p53*** plays a central role in a signal transduction pathway that mediates G-1 arrest after ***DNA*** ***damage*** , though the mechanism by which G-1 arrest occurs has not been elucidated.
The cyclin-associated protein p21-waf1/cip1 has recently been shown to be induced by ***p53*** and to ***inhibit*** cyclin complex-mediated phosphorylation of pRB in vitro. Thus, we investigated a possible role for pRB in the ***p53*** -mediated ***DNA*** ***damage*** response.
After gamma-irradiation, cells ***expressing*** wild-type ***p53*** arrested in G-1, contained increased levels of WAF1/CIP1 mRNA, and demonstrated accumulation of hypophosphorylated pRB. In contrast, cell lines with abnormal ***p53*** genes or with ***p53*** functionally inactivated by the E6 oncoprotein of HPV16 (a high-risk HPV) failed to arrest in G-1, did not elevate WAF1/CIP1 mRNA, and did not accumulate hypophosphorylated pRB. Despite apparently normal elevation of ***p53*** protein and WAF1/CIP1 mRNA after irradiation, cells ***expressing*** HPV16 E7 also failed to arrest in G-1 and did not accumulate hypophosphorylated pRB. Disruption of RB genes alone did not totally abrogate this G-1 arrest. Our results suggest that ***p53*** indirectly regulates phosphorylation of pRB and that pRB and/or other pRB-like molecules that bind to HPV16 E7 participate in the ***DNA*** ***damage*** -mediated G-1 arrest signal. In the process of HPV infection, the HPV E6 and E7 oncoproteins may undermine this cell cycle checkpoint, contributing to the accumulation of genetic alterations during tumorigenesis.

L10 ANSWER 5 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
ACCESSION NUMBER: 1994:302570 BIOSIS
DOCUMENT NUMBER: PREV199497315570
TITLE: Growth arrest by induction of ***p53*** in ***DNA*** ***damaged*** keratinocytes is bypassed by human papillomavirus 16 E7.
AUTHOR(S): Demers, G. William; Foster, Scott A.; Halbert, Christine L.; Galloway, Denise A.
CORPORATE SOURCE: Cell Biol. Program, Fred Hutchinson Cancer Res. Center, 1124 Columbia Street, C1-015, Seattle, WA 98104 USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1994) Vol. 91, No. 10, pp. 4382-4386.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Cellular ***tumor*** suppressors ***p53*** and Rb play an important role in controlling cell proliferation. Inactivation of these ***tumor*** suppressor proteins can occur by gene mutation or by association with oncoproteins from the small DNA ***tumor*** viruses.
One function of ***p53*** is in regulating cell cycle checkpoint control after ***DNA*** ***damage*** . To dissect the pathways by which ***p53*** and Rb may act, the E6 and E7 oncogenes of human papillomavirus (HPV) types 6 and 16 were introduced into primary human epithelial cells by retroviral transfer vector, and cells were assayed for growth arrest after ***DNA*** ***damage*** induced by actinomycin
D. The E6 or E7 oncogenes from the low-risk HPV6 had no affect on growth
arrest, ***p53*** protein levels increased, Rb protein levels decreased, and Rb was predominantly in the hypophosphorylated state similar to vector-infected cells. Either the E6 or the E7 oncogene from the high-risk HPV16 abrogated growth arrest. Cells ***expressing*** HPV16 E6 (16E6) were severely ***reduced*** in ***p53*** protein
levels that did not increase detectably after ***DNA*** ***damage***
, Rb protein levels did not decrease, and hyperphosphorylated Rb was present. After ***DNA*** ***damage*** in cells ***expressing***
16E7 ***p53*** levels increased, and Rb protein levels decreased; however, Rb was predominantly in the hyperphosphorylated state. Even though ***p53*** protein levels increased in response to ***DNA*** ***damage*** in cells ***expressing*** 16E7, G, growth arrest was bypassed. This suggests that the circuitry controlling the growth arrest signal after ***DNA*** ***damage*** may be interconnected between
the ***p53*** and Rb pathways.

L10 ANSWER 6 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
ACCESSION NUMBER: 1995:37710 BIOSIS
DOCUMENT NUMBER: PREV199598052010
TITLE: Induction of bax by genotoxic stress in human cells correlates with normal ***p53*** status and apoptosis.
AUTHOR(S): Zhan, Qimin; Fan, Sajan; Bae, Insoo; Guillouf, Christel; Liebermann, Dan A.; O'Connor, Patrick M.; Fornance, Albert J., Jr. (1)
CORPORATE SOURCE: (1) Lab. Mol. Pharmacol., Dev. Ther. Program, Div. Cancer Treatment, Natl. Cancer Inst., Build. 37, Room 5C09, Bethesda, MD 20892 USA
SOURCE: Oncogene, (1994) Vol. 9, No. 12, pp. 3743-3751.
ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
AB ***DNA*** - ***damaging*** agents such as ionizing radiation (IR) activate the ***tumor*** suppressor ***p53*** and in some cases can cause apoptosis. M1 cells, which do not ***express*** the endogenous ***tumor*** suppressor gene ***p53*** , undergo apoptosis following activation of a temperature sensitive ***p53*** transgene, where it has been shown that bax, an important mediator of apoptosis, is a ***p53*** target gene (Selvakumaran et al, Oncogene 9, 1791-8, 1994). Since ***p53*** can function as a transcription factor after activation by IR, the genetic response to this stress was examined

in a panel of human cells with defined ***p53*** status. Like the ***p53*** -regulated gene gadd45, bax was rapidly induced, as measured by increased mRNA levels, in the ***p53*** wt (wild type) human myeloid line ML-1, and it was not induced in cells lacking functional ***p53*** . However, unlike other ***p53*** -regulated genes, bax was only induced in ***p53*** wt cells in which IR also triggered apoptosis. In the case of bcl2, which opposes bax function, mRNA levels were ***reduced*** in ML-1 cells after IR. Thus, bax appears to be an unique ***p53*** -regulated gene in that its induction by IR not only requires functional ***p53*** but also requires that the cells be apoptosis "proficient."

L10 ANSWER 7 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94243751 EMBASE
DOCUMENT NUMBER: 1994243751
TITLE: Cell cycle arrests and radiosensitivity of human ***tumor*** cell lines: Dependence on wild-type ***p53*** for radiosensitivity.
AUTHOR: McIlwrath A.J.; Vasey P.A.; Ross G.M.; Brown R.
CORPORATE SOURCE: CRC Department of Medical Oncology, CRC Beatson Laboratories, Garscube Estate, Switchback Road,Bearsden Glasgow G61 1BD, United Kingdom
SOURCE: Cancer Research, (1994) 54/14 (3718-3722). ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 014 Radiology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Loss of ***p53*** function has been shown to cause increased resistance to ionizing radiation in normal murine cells; however, the role of ***p53*** in radioresistance of human ***tumor*** cells is less clear. Since wild-type ***p53*** function is required for radiation-induced G1 arrest, we measured G1 arrest in 12 human ***tumor*** cell lines that have a wide range of radiosensitivities (surviving fraction at 2 Gy, 0.11-0.8). We observed a significant correlation between the level of ionizing radiation-induced G1 arrest and radiosensitivity. Cell lines having G1 arrest are more radiosensitive. There is no correlation between maximal G2 arrest and radiosensitivity. ***Expression*** of a dominant-negative mutant of ***p53*** (codon 143, Val to Ala) in transfectants of the radiosensitive human ovarian cell line A2780 abrogates the radiation- induced G1 arrest. Such mutant ***p53*** transfectants are more resistant to ionizing radiation than the parental line and vector-alone transfectants, as measured by clonogenic assays. These results support the concept that wild- type ***p53*** function is required for sensitivity of ***tumor*** cells to ***DNA*** - ***damaging*** agents, such as ionizing radiation, and that the loss of ***p53*** function in certain human ***tumor*** cells can lead to resistance to ionizing radiation.

L10 ANSWER 8 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94142815 EMBASE
DOCUMENT NUMBER: 1994142815
TITLE: ***p53*** and E2F-1 cooperate to mediate apoptosis.
AUTHOR: Wu X.; Levine A.J.
CORPORATE SOURCE: Department of Molecular Biology, Princeton University,Princeton, NJ 08544-1014, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1994) 91/9 (3602-3606). ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The ***tumor*** -suppressor protein ***p53*** appears to function at the G1 phase of the cell cycle as a checkpoint in response to ***DNA*** ***damage*** . Mutations in the ***p53*** gene lead to an increased rate of genomic instability and tumorigenesis. The E2F-1 transcription factor is a protein partner of the retinoblastoma-susceptibility gene product, RB. E2F-1 appears to function as a positive regulator or signal for entry into S phase. To explore possible interactions of ***p53*** and E2F-1 in the cell cycle, a human E2F-1 ***expression*** plasmid was introduced into a murine cell line containing a temperature-sensitive ***p53*** allele which produces a ***p53*** protein in the wild-type conformation at 32.degree.C and the mutant form at 37.5.degree.C. Coexpression of the wild-type ***p53*** protein and E2F-1 in these cells resulted in a rapid loss of cell viability through a process of apoptosis. Thus, the cell cycle utilizes an interacting or communicative pathway between RB-E2F-1 and ***p53*** .

L10 ANSWER 9 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 6
ACCESSION NUMBER: 94229848 EMBASE
DOCUMENT NUMBER: 1994229848
TITLE: Induction of WAF1/CIP1 by a ***p53*** -independent pathway.
AUTHOR: Michieli P.; Chedid M.; Lin D.; Pierce J.H.; Mercer W.E.; Givol D.
CORPORATE SOURCE: Cellular/Molecular Biology Lab., National Cancer Institute, NIH,Bethesda, MD 20892, United States
SOURCE: Cancer Research, (1994) 54/13 (3391-3395). ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The ***p53*** -inducible gene WAF1/CIP1 encodes a M(r) 21,000 protein (p21) that has been shown to arrest cell growth by ***inhibition*** of cyclin-dependent kinases. Induction of WAF1/CIP1 in cells undergoing ***p53*** -dependent G1 arrest or apoptosis supports the idea that WAF1/CIP1 is a critical downstream effector of ***p53*** . In the present study, we used embryonic fibroblasts from ***p53*** 'knock-out' mice to demonstrate ***p53*** -independent induction of WAF1/CIP1. We show that serum or individual growth factors such as platelet-derived growth factor, fibroblast growth factor, and epidermal growth factor but not insulin are able to induce WAF1/CIP1 in quiescent ***p53*** -deficient cells as well as in normal cells. The kinetics of this transient induction, which is enhanced by cycloheximide, demonstrates that WAF1/CIP1 is an immediate-early gene the transcript of which reaches a peak at approximately 2 h following serum or growth factor stimulation. On the other hand, ***DNA*** ***damage*** elicited by .gamma.-irradiation induces WAF1/CIP1 in normal human and mouse fibroblasts but does not affect WAF1/CIP1 ***expression*** in ***p53*** -deficient cells. These results suggest the existence of two separate pathways for the induction of WAF1/CIP1, a ***p53*** - dependent one activated by ***DNA*** ***damage*** and a ***p53*** -independent one activated by mitogens at the entry into the cell cycle. The possible function of p21 at this early stage is discussed.

L10 ANSWER 10 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94346462 EMBASE
DOCUMENT NUMBER: 1994346462
TITLE: The carboxy-terminal serine 392 phosphorylation site of human ***p53*** is not required for wild-type activities.
AUTHOR: Fiscella M.; Zambrano N.; Ullrich S.J.; Unger T.; Lin D.; Cho B.; Mercer W.E.; Anderson C.W.; Appella E.
CORPORATE SOURCE: Laboratory of Cell Biology, National Institute of Health,Bethesda, MD 20892, United States
SOURCE: Oncogene, (1994) 9/11 (3249-3257). ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Wild-type ***p53*** functions in the G1 ***DNA*** ***damage***
checkpoint pathway by activating gene transcription and preventing cell cycle progression. Others reported that mutation of the serine 386 codon in mouse ***p53*** abolished its ability to suppress growth. Serine 386 of murine ***p53*** and the homologous residue of human ***p53*** , serine 392, are phosphorylated in vivo and can be phosphorylated in vitro by casein kinase II (CKII). We constructed mutants
that changed serine 392 of human ***p53*** to alanine (***p53*** -S392A) or aspartic acid (***p53*** -S392D); cotransfection of both these mutants with a reporter gene carrying a ***p53*** -responsive element into the ***p53*** -null Saos-2 cell line activated transcription as well as did wild-type ***p53*** . Furthermore, both mutants blocked cell cycle progression after transient transfection in these cells. A stable derivative of the T98G human glioblastoma cell line was established that ***expressed*** ***p53*** -S392A in response to dexamethasone. Overexpression of this mutant activated transcription of the endogenous waf1 (also called cipl) and mdm2 genes to the same extent as wild-type ***p53*** and also produced growth arrest. Finally, ***p53*** -S392A and ***p53*** -S392D suppressed foci formation by
activated ras and adenovirus E1A oncogenes as efficiently as did wild-type
p53 . Thus, unlike mutants that altered the serine 15 phosphorylation site, elimination of the serine 392 phosphorylation site had no discernible effect on ***p53*** function. We conclude that neither phosphorylation nor RNA attachment to serine 392 are required for human ***p53*** 's ability to suppress cell growth or to activate transcription in vivo.

L10 ANSWER 11 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94305394 EMBASE
DOCUMENT NUMBER: 1994305394
TITLE: Xenopus ***p53*** is biochemically similar to the human tumour suppressor protein ***p53*** and is induced upon ***DNA*** ***damage*** in somatic cells.
AUTHOR: Cox L.S.; Midgley C.A.; Lane D.P.
CORPORATE SOURCE: CRC Cell Transformtn Research Group, Department of
Biochemistry, University of Dundee,Dundee DD1 4HN, United Kingdom
SOURCE: Oncogene, (1994) 9/10 (2951-2959).
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Xenopus ***p53*** cDNA, homologous to the human tumour suppressor
p53 , has previously been cloned from oocyte and gastrula libraries. In this report, we describe a polyclonal antibody 2674 raised against Xenopus ***p53*** (Xp53) ***expressed*** in bacteria, that
recognises proteins of approximately 52, 46 and 35 kDa present in Xenopus
oocytes, parthenogenically activated eggs and in somatic tissue culture cells. We report here purification of Xp53 from insect cells infected with Xp53-baculovirus, and this protein is shown to be phosphorylated by casein
kinase II but has low sequence-specific DNA binding activity. Using similar purification conditions, we have isolated endogenous Xp53, showing
that Xenopus eggs contain high levels of ***p53*** protein. Xp53 from eggs binds to the ***p53*** -specific DNA-binding consensus sequence.
Two dimensional gel analysis indicates that Xp53 from eggs may exist in various states of phosphorylation. u.v.-induced ***DNA*** ***damage*** of somatic Xenopus cells results in accumulation of Xp53.
We suggest that the high levels of putative Xp53 detected in eggs may represent maternal stockpiles of a protein necessary to protect rapidly dividing cells from the effects of ***DNA*** ***damage*** .

L10 ANSWER 12 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
ACCESSION NUMBER: 1994:222559 BIOSIS
DOCUMENT NUMBER: PREV199497235559
TITLE: Interactions between ***p53*** and MDM2 in a mammalian
cell cycle checkpoint pathway.
AUTHOR(S): Chen, Chaw-Yuan; Oliner, Jonathan D.; Zhan, Qimin; Fornace., Albert J., Jr.; Vogelstein, Bert; Kastan, Michael B. (1)
CORPORATE SOURCE: (1) Johns Hopkins Oncology Center, Baltimore, MD 21287 USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1994) Vol. 91, No. 7, pp. 2684-2688.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Normal ***p53*** function is required for optimal arrest of cells in the G-1 phase of the cell cycle following certain types of ***DNA*** ***damage*** . Loss of this cell cycle checkpoint may contribute to ***tumor*** development by increasing the number of genetic abnormalities in daughter cells following ***DNA*** ***damage***
.
The MDM2 protein is an endogenous gene product that binds to the ***p53*** protein and is able to block ***p53*** -mediated transactivation of cotransfected reporter constructs; thus, interactions between MDM2 and ***p53*** in this checkpoint pathway following ionizing irradiation were examined. Though increases in ***p53*** protein by ***DNA*** ***damage*** were not abrogated by MDM2
overexpression, increased levels of MDM2, resulting either from endogenous
gene amplification or from transfection of an exogenous ***expression***
vector, were associated with a ***reduction*** in the ability of cells to arrest in G-1 following irradiation. In addition, ***expression*** of endogenous MDM2 was enhanced by ionizing irradiation at the level of transcription in a ***p53*** -dependent fashion. These observations demonstrate that MDM2 overexpression can ***inhibit*** ***p53*** function in a known physiologic pathway and are consistent with the hypothesis that MDM2 may function in a "feedback loop" mechanism with
p53 , possibly acting to limit the length or severity of the ***p53*** -mediated arrest following ***DNA*** ***damage*** .

L10 ANSWER 13 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94108080 EMBASE
DOCUMENT NUMBER: 1994108080
TITLE: The gadd and MyD genes define a novel set of mammalian genes encoding acidic proteins that synergistically suppress cell growth.
AUTHOR: Zhan Q.; Lord K.A.; Alamo Jr. I.; Hollander M.C.; Carrier
F.; Ron D.; Kohn K.W.; Hoffman B.; Liebermann D.A.; Fornace Jr. A.J.
CORPORATE SOURCE: Laboratory of Molecular Pharmacology, NCI, Bldg.
37,Bethesda, MD 20892, United States
SOURCE: Molecular and Cellular Biology, (1994) 14/4 (2361-2371).
ISSN: 0270-7306 CODEN: MCEBD4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A remarkable overlap was observed between the gadd genes, a group of often
coordinately ***expressed*** genes that are induced by genotoxic stress and certain other growth arrest signals, and the MyD genes, a set of myeloid differentiation primary response genes. The MyD116 gene was found to be the murine homolog of the hamster gadd34 gene, whereas

MyD118
and gadd45 were found to represent two separate but closely related genes.
Furthermore, gadd34/MyD116, gadd45, MyD118, and gadd153 encode acidic
proteins with very similar and unusual charge characteristics; both this property and a similar pattern of induction are shared with mdm2, which, like gadd45, has been shown previously to be regulated by the ***tumor*** suppressor ***p53*** . ***Expression*** analysis revealed that they are distinguished from other growth arrest genes in that they are ***DNA*** ***damage*** inducible and suggests a role
for these genes in growth arrest and apoptosis either coupled with or uncoupled from terminal differentiation. Evidence is also presented for coordinate induction in vivo by stress. The use of a short-term transfection assay, in which ***expression*** vectors for one or a combination of these gadd/MyD genes were transfected with a selectable marker into several different human ***tumor*** cell lines, provided direct evidence for the growth-inhibitory functions of the products of these genes and their ability to synergistically suppress growth. Taken together, these observations indicate that these genes define a novel class of mammalian genes encoding acidic proteins involved in the control of cellular growth.

L10 ANSWER 14 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 8
ACCESSION NUMBER: 94114072 EMBASE
DOCUMENT NUMBER: 1994114072
TITLE: Wild-type ***p53*** gene ***expression*** induces granulocytic differentiation of HL- 60 cells.
AUTHOR: Soddu S.; Blandino G.; Citro G.; Scardigli R.; Piaggio G.; Ferber A.; Calabretta B.; Sacchi A.
CORPORATE SOURCE: Molecular Oncogenesis Laboratory, Istituto Regina Elena
CRS, Via delle Messi d'oro 156,00158 Rome, Italy
SOURCE: Blood, (1994) 83/8 (2230-2237).
ISSN: 0006-4971 CODEN: BLOOAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology
025 Hematology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Overexpression of wild-type ***p53*** gene in malignant cell lines has
been shown to ***inhibit*** cell proliferation in a number of cases. However, endogenous ***p53*** protein seems to play little role in normal cell-cycle control as suggested by the normal development of ***p53*** null mice, and by the low ***p53*** protein levels ***expressed*** in most cell types. Recently, increased ***expression*** of endogenous ***p53*** protein has been observed
during the cellular response to ***DNA*** ***damage*** , as well as
during differentiation of human hematopoietic cells. To study the role of the ***p53*** gene in hematopoietic differentiation, we introduced the wild-type ***p53*** gene or the temperature-sensitive ***p53*** (Val135) mutant into ***p53*** -deficient HL-60 promyelocytic leukemia
cells. Morphological analysis, flow-cytometric determination of granulocytic or monocytic surface markers, and ability to ***reduce*** nitroblue tetrazolium (NBT) demonstrated that ***expression*** of exogenous wild-type ***p53*** gene in HL-60 cells induces differentiation through the granulocytic pathway. Proliferation and cell-cycle analysis performed early after ***expression*** of wild-type ***p53*** showed that induction of differentiation is not coupled with growth arrest, which suggests that ***p53*** is involved in differentiation independently of its activity on the cell cycle.

L10 ANSWER 15 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:451874 BIOSIS
DOCUMENT NUMBER: PREV199497464874
TITLE: Regulation of mdm2 ***expression*** by ***p53*** : Alternative promoters produce transcripts with nonidentical translation potential.
AUTHOR(S): Barak, Yaacov; Gottlieb, Eyal; Juven-Gershon, Tamar; Oren, Moshe (1)
CORPORATE SOURCE: (1) Dep. Chemical Immunology, Weizmann Inst. Sci., Rehovot
76100 Israel
SOURCE: Genes & Development, (1994) Vol. 8, No. 15, pp. 1739-1749.
ISSN: 0890-9369.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The mdm2 proto-oncogene product binds to the ***p53*** ***tumor***
suppressor protein and ***inhibits*** its ability to trans-activate target genes. One such target gene is mdm2 itself, which is therefore considered a component of a ***p53*** negative feedback loop. Two tandem ***p53*** -binding motifs residing within the first intron of the murine mdm2 gene confer upon it ***p53*** -mediated activation. We
now report that in murine cells ***p53*** activates an internal mdm2 promoter (P-2) located near the 3' end of intron 1, resulting in mRNA whose transcription starts within exon 2. P-2 is activated by ***p53*** within artificial constructs, as well as within the context of the chromosomal mdm2 gene. Activation follows either the introduction of overexpressed wild-type ***p53*** into cells or the induction of endogenous wild-type ***p53*** by ionizing radiation. The upstream, constitutive (P-1) mdm2 promoter is only mildly affected by ***p53*** , if at all. The ***p53*** -derived mdm2 transcripts lack exon 1 and a few nucleotides from exon 2. As the first in-frame AUG of mdm2 is located
within exon 3, the two types of mdm2 transcripts should possess similar coding potentials. Nevertheless, in vitro conditions, where each of these transcripts yields a distinct translation profile, reflect the differential usage of translation initiation codons. Initiation of translation at internal AUG codons, which occurs also in vivo, gives rise to MDM2 polypeptides incapable of binding to ***p53*** . In vitro translation profiles of the various mdm2 transcripts could be manipulated by changing the amounts of input RNA. Thus, ***p53*** can modulate both the amount and the nature of MDM2 polypeptides through activation of
the internal P-2 promoter.

L10 ANSWER 16 OF 36 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 95064014 MEDLINE
DOCUMENT NUMBER: 95064014 PubMed ID: 7973727
TITLE: Interaction of the ***p53*** -regulated protein Gadd45 with proliferating cell nuclear antigen.
COMMENT: Comment in: Science. 1994 Nov 25;266(5189):1321-2
Comment in: Science. 1995 Nov 10;270(5238):1003-4; discussion 1005-6
Comment in: Science. 1995 Nov 10;270(5238):1004-5; discussion 1005-6
AUTHOR: Smith M L; Chen I T; Zhan Q; Bae I; Chen C Y; Gilmer T M;
Kastan M B; O'Connor P M; Fornace A J Jr
CORPORATE SOURCE: Laboratory of Molecular Pharmacology, National Cancer
Institute, Bethesda, MD 20892.
CONTRACT NUMBER: ES05777 (NIEHS)
SOURCE: SCIENCE, ***(1994 Nov 25)*** 266 (5189) 1376-80.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19960321
Entered Medline: 19941223
AB GADD45 is a ubiquitously ***expressed*** mammalian gene that is induced by ***DNA*** ***damage*** and certain other stresses. Like
another ***p53*** -regulated gene, p21WAF1/CIP1, whose product binds to
cyclin-dependent kinases (Cdk's) and proliferating cell nuclear antigen (PCNA), GADD45 has been associated with growth suppression. Gadd45 was
found to bind to PCNA, a normal component of Cdk complexes and a protein
involved in DNA replication and repair. Gadd45 stimulated DNA excision

repair in vitro and ***inhibited*** entry of cells into S phase. These results establish GADD45 as a link between the ***p53*** -dependent cell cycle checkpoint and DNA repair.

L10 ANSWER 17 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94102008 EMBASE
DOCUMENT NUMBER: 1994102008
TITLE: WAF1/CIP1 is induced in ***p53*** -mediated G1 arrest and apoptosis.
AUTHOR: El-Deiry W.S.; Harper J.W.; O'Connor P.M.; Velculescu V.E.;
Canman C.E.; Jackman J.; Pietenpol J.A.; Burrell M.; Hill D.E.; Wang Y.; Wiman K.G.; Mercer W.E.; Kastan M.B.; Kohn K.W.; Elledge S.J.; Kinzler K.W.; Vogelstein B.
CORPORATE SOURCE: Human Genetics/Molecular Biol. Prog., Oncology Center,
Johns Hopkins Univ. Sch. of Medicine,Baltimore, MD 21231, United States
SOURCE: Cancer Research, (1994) 54/5 (1169-1174).
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The ***tumor*** growth suppressor WAF1/CIP1 was recently shown to be
induced by ***p53*** and to be a potent inhibitor of cyclin-dependent kinases. In the present studies, we sought to determine the relationship between the ***expression*** of WAF1/CIP1 and endogenous regulation of
p53 function. WAF1/CIP1 protein was first localized to the nucleus
of cells containing wild-type ***p53*** and undergoing G1 arrest. WAF1/CIP1 was induced in wild-type ***p53*** -containing cells by exposure to ***DNA*** ***damaging*** agents, but not in mutant ***p53*** -containing cells. The induction of WAF1/CIP1 protein occurred
in cells undergoing either ***p53*** -associated G1 arrest or apoptosis but not in cells induced to arrest in G1 or to undergo apoptosis through ***p53*** -independent mechanisms. ***DNA*** ***damage*** led to
increased levels of WAF1/CIP1 in cyclin E-containing complexes and to an
associated decrease in cyclin-dependent kinase activity. These results support the idea that WAF1/CIP1 is a critical downstream effector in the ***p53*** - specific pathway of growth control in mammalian cells.

L10 ANSWER 18 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10
ACCESSION NUMBER: 1994:228021 BIOSIS
DOCUMENT NUMBER: PREV199497241021
TITLE: Introduction of wild-type ***p53*** in a human ovarian ***cancer*** cell line not ***expressing*** endogenous ***p53*** .
AUTHOR(S): Vikhanskaya, Faina; Erba, Eugenio; D'Incalci, Maurizio; Broggini, Massimo (1)
CORPORATE SOURCE: (1) Ist. Ricerche Farmacol. 'Mario Negri', via Eritrea 62,
20157 Milan Italy
SOURCE: Nucleic Acids Research, (1994) Vol. 22, No. 6, pp. 1012-1017.
ISSN: 0305-1048.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Utilizing a temperature sensitive ***p53*** mutant (pLTRp53cGval135)
which ***expresses*** mutant ***p53*** at 37 degree C and a wild-type like ***p53*** at 32 degree C we transfected a human ovarian
cancer cell line (SKOV3) which does not ***express*** endogenous ***p53*** . Among the different clones obtained, we selected
three clones. Two were obtained from simultaneous transfection of ***p53*** and neomycin resistance ***expression*** plasmids (SK23a
and SK9), the other was obtained from transfection experiments utilizing the neomycin resistance gene only (SKN). Introduction of mutant ***p53*** did not alter the morphology or growth characteristics of this ovarian ***cancer*** cell line. Upon shifting to the permissive temperature, a dramatic change in morphology and growth rate was observed
in SK23a and SK9 cells that is associated with the presence of a wild-type like ***p53*** . SKN and SKOV3 cells maintained at 32 degree C did not
change morphology and only slightly ***reduced*** proliferation. Both SK23a and SK9 cells did not show evidence of apoptosis when measured up to
72 hours of maintenance at 32 degree C. In contrast to what observed in other cell lines, SK23a and SK9 cells maintained at 32 degree C were not blocked in G1, but they were accumulated in G2-M. This accumulation was
transient and could be due either to a blockade or to a delay in the G2 progression. No down-regulation of c-myc was observed in ***p53*** ***expressing*** clones when shifted to the permissive temperature. In these conditions gadd45 mRNA ***expression*** was highly stimulated in
SK9 and SK23a cells but not in SKN cells. In both clones Gas 1 mRNA was
not detected either at 37 degree C or 32 degree C. This system represents a new and useful model for studying the effect of the absence of ***p53*** (SKOV3 or SKN), presence of mutated ***p53*** (SK23a and
SK9 kept at 37 degree C) or wild type ***p53*** (SK23a and SK9 kept at
32 degree C) on the mechanism of response of ***cancer*** cells to ***DNA*** ***damaging*** agents.

L10 ANSWER 19 OF 36 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:651975 HCAPLUS
DOCUMENT NUMBER: 121:251975
TITLE: ***P53*** ***tumor*** suppressor gene
AUTHOR(S): Yamaguchi, Nobuo
CORPORATE SOURCE: Inst. Med. Sci., Univ. Tokyo, Tokyo, 108, Japan
SOURCE: Baiosaiensu to Indasutori (***1994***), 52(9), 736-7
CODEN: BIDSE6; ISSN: 0914-8981
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, with 7 refs., on the mechanisms of G1 arrest by p21 protein upon
DNA ***damage*** ; ***DNA*** ***damage*** , increment in
intracellular ***p53*** level, increment in p21 level by binding of ***p53*** to the ***expression*** regulation region of p21, ***inhibition*** of cyclin dependent kinase by p21 binding, decrease in phosphorylation level of Rb, and G1 arrest.

L10 ANSWER 20 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
11
ACCESSION NUMBER: 1994:129567 BIOSIS
DOCUMENT NUMBER: PREV199497142567
TITLE: ***DNA*** ***damage*** induced ***p53*** mediated transcription is ***inhibited*** by human papillomavirus type 18 E6.
AUTHOR(S): Gu, Zhengming; Pim, David; Labrecque, Sylvie; Banks, Lawrence; Matlashewski, Greg (1)
CORPORATE SOURCE: (1) Inst. Parasitol., McGill Univ., 21,111 Lakeshore Rd.,
Ste. Anne de Bellevue, PQ H9X 3V9 Canada
SOURCE: Oncogene, (1994) Vol. 9, No. 2, pp. 629-633.
ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Cervical ***cancer*** is similar to other human cancers in that it develops through a multistep process. However, infection with oncogenic human papillomaviruses (HPVs) is believed to be essential for the initiation of this disease. Although HPV may play a central role in the early stages of neoplasia, the accumulation of mutations in an assortment of genes precedes the development of malignant cervical carcinoma. The

mechanisms by which abnormalities accumulate are various, but it is possible that viral proteins are involved. In particular, the viral E6 oncoprotein has been shown to interact with the cellular tumour suppressor protein ***p53*** , which is involved in ***DNA*** ***damage*** repair pathways. Hence, E6 may contribute to the genomic instability through this interaction with ***p53*** . We have tested this hypothesis by monitoring the effects of E6 upon ***DNA*** ***damage*** induced ***p53*** transcriptional activity. This study shows that HPV-18 E6 ***inhibits*** ***p53*** transcriptional activity following genotoxic stress with UV radiation. No effect was observed when a mutant E6 unable to direct the degradation of ***p53*** was included in this assay. These results suggest that continued E6 ***expression*** may contribute to the accumulation of ***DNA*** ***damage*** associated with the progression of cervical ***cancer***

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L10 ANSWER 21 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 12
ACCESSION NUMBER: 94377361 EMBASE
DOCUMENT NUMBER: 1994377361
TITLE: ***p53*** Immunostaining positivity is associated with ***reduced*** survival and is imperfectly correlated with gene mutations in resected non-small cell lung ***cancer*** : A preliminary report of LCSG 871.
AUTHOR: Carbone D.P.; Mitsudomi T.; Chiba H.; Piantadosi S.; Rusch V.; Nowak J.A.; McIntire D.; Slamon D.; Gazdar A.; Minna J.
CORPORATE SOURCE: UT Southwestern Med Ctr, 5323 Harry Hines,Dallas, TX 75235-8593, United States
SOURCE: Chest, (1994) 106/6 SUPPL. (377S-381S). ISSN: 0012-3692 CODEN: CHETBF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We investigated the correlation of ***p53*** abnormalities with survival in 85 patients with non-small cell lung ***cancer*** (NSCLC) who had undergone resection with curative intent as part of Lung ***Cancer*** Study Group (LCSG) 871. Our previous studies showed that only a subset of ***p53*** mutations in lung cancers result in overexpression. In addition, protein overexpression has been described in the absence of mutation. Therefore, we determined both ***p53*** protein overexpression (by immunostaining) and ***p53*** and ras gene mutations (by single-strand conformation polymorphism and DNA sequencing) in this set of resected ***tumor*** specimens. Clinical follow-up data were available for 75 cases. Of the studied patients, 64% showed ***p53*** overexpression and 51% had mutant ***p53*** sequences; however, the concordance rate was only 67%. There was a negative survival correlation with positive ***p53*** immunostaining (p=0.05), but not with the presence of gene mutations (p=0.62) in this group of patients. Overexpression of ***p53*** protein determined by immunostaining may contribute to adverse outcome due to the ability of ***p53*** to act as a dominant oncogene, or alternatively, overexpression may reflect ongoing ***DNA*** ***damage*** in the ***tumor*** as a marker for a more aggressive behavior. When adjusted for stage, age, and gender by multivariate analysis, however, there was no independent impact of ***p53*** overexpression on survival.

L10 ANSWER 22 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95040251 EMBASE
DOCUMENT NUMBER: 1995040251
TITLE: The protooncogene CHOP/GADD153, involved in growth arrest and ***DNA*** ***damage*** response, is amplified in a subset of human sarcomas.
AUTHOR: Forus A.; Florenes V.A.; Maelandsmo G.M.; Fodstad O.; Myklebost O.
CORPORATE SOURCE: Department of Tumor Biology, Institute for Cancer Research, Norwegian Radium Hospital,Montebello, N-0310 Oslo, Norway
SOURCE: Cancer Genetics and Cytogenetics, (1994) 78/2 (165-171). ISSN: 0165-4608 CODEN: CGCYDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The C/EBP-homologous transcription factor CHOP (GADD153) is inducible by growth ***inhibition*** or ***DNA*** ***damage*** , and has been shown to be oncogenically activated by the specific (12;16) translocation in human myxoid liposarcoma. We have now found CHOP amplification in two sarcoma cell lines with previously reported amplification of the nearby GLI gene. Among 98 other human sarcomas of various types, CHOP was amplified in a hemangiopericytoma, a liposarcoma, and two osteosarcomas. High constitutive ***expression*** levels of CHOP were observed in tumors with gone amplification, but also in some other samples. The nearby MDM2 gene, which codes for a protein that may inactivate wild-type ***p53*** , has previously been reported to be frequently amplified in sarcoma. In our sarcoma panel, MDM2 was amplified in 9 cases. MDM2 and CHOP were co-amplified in two of these, whereas the two osteosarcomas had amplified CHOP but not MDM2. CHOP was amplified in both cell lines with GLI amplification, and MDM2 only in one. No mutations in the TP53 gene have been found in samples with amplification of MDM2. In contrast, the cell line in which CHOP but not MDM2 was amplified had mutated TP53, suggesting that selection of this amplicon was not mediated through ***p53*** inactivation.

L10 ANSWER 23 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94342002 EMBASE
DOCUMENT NUMBER: 1994342002
TITLE: Evidence for a ***p53*** -independent pathway for upregulation of SDI1/CIP1/WAF1/p21 RNA in human cells.
AUTHOR: Johnson M.; Dimitrov D.; Vojta P.J.; Barrett J.C.; Noda A.; Pereira-Smith O.M.; Smith J.R.
CORPORATE SOURCE: Huffington Center on Aging, Division of Molecular Virology, Baylor College of Medicine, One Baylor Plaza,Houston, TX 77030, United States
SOURCE: Molecular Carcinogenesis, (1994) 11/2 (59-64). ISSN: 0899-1987 CODEN: MOCAE8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB SDI1 is an inhibitor of DNA synthesis that we isolated by ***expression*** screening cDNAs prepared from senescent, terminally nondividing human cells. Other groups then cloned this gene as a cyclin-dependent kinase (cdk)-interacting protein (CIP1, p21) that ***inhibits*** cdks; the gene was also isolated by screening for genes transactivated by ***p53*** (WAF1). ***p53*** levels are low in senescent and quiescent contact- ***inhibited*** or serum-deprived normal human cells, which we have found ***express*** high levels of SDI1 mRNA. This indicates that alternate pathways for upregulation of

message level of this gene may exist. We therefore proceeded with the study presented here, treating human cells with a variety of growth-arrest-inducing agents, including some that damaged DNA, and found that RNA levels of SDI1 were increased in all cases that resulted in growth ***inhibition*** . More important, with the exception of .gamma.-radiation, most of these agents were able to elevate SDI1 message levels in cells lacking wild-type ***p53*** . At least two distinct kinetic profiles for RNA induction were observed, one that implicated ***p53*** transactivation and occurred early enough to cause arrest, and another that clearly was ***p53*** independent and suggested a role for the SDI1 gene product in the maintenance rather than in the cause of ***inhibition*** of DNA synthesis.

L10 ANSWER 24 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 13
ACCESSION NUMBER: 1993:365729 BIOSIS
DOCUMENT NUMBER: PREV199396051404
TITLE: Induction of cellular ***p53*** activity by ***DNA*** - ***damaging*** agents and growth arrest.
AUTHOR(S): Zhan, Qimin; Carrier, France; Fornace, Albert J., Jr. (1)
CORPORATE SOURCE: (1) Lab. Mol. Pharmacol., DTP, DCT, Natl. Cancer Inst., Room 5C09, Build. 37, Bethesda, MD 20892 USA
SOURCE: Molecular and Cellular Biology, (1993) Vol. 13, No. 7, pp. 4242-4250.
ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The ***tumor*** suppressor ***p53*** can function as a sequence-specific transcription factor and is required for activation by ionizing radiation (IR) of one or more downstream effector genes, such as the human GADD45 gene. One important consequence of IR that is probably mediated by these downstream effector genes is activation of the ***p53*** -mediated G-1 cell cycle checkpoint. While the induction of reporter constructs containing ***p53*** -binding sites has already been demonstrated with ***p53*** ***expression*** vectors, we have now demonstrated the direct activation of such a construct after treatment of the human RKO line, which has a normal ***p53*** phenotype, with various types of ***DNA*** - ***damaging*** agents and also after growth arrest produced by medium depletion (starvation). IR, UV radiation, and methylmethane sulfonate were found to induce ***p53*** activity when a stably integrated reporter construct containing functional ***p53*** -binding sites was used and also in mobility shift assays with a ***p53*** -binding site from the GADD45 gene, and IR-inducible gene previously associated with growth arrest. The same cell treatments that induced this ***p53*** activity also caused an increase in cellular ***p53*** protein levels. The response in cells lacking normal ***p53*** or in RKO cells ***expressing*** a dominant negative mutant ***p53*** was markedly ***reduced*** . Interestingly, the spectrum of effective inducing agents for the above-described experiments was similar to that which induces GADD45 either in cells with a normal ***p53*** status or, with the exception of IR, in cells lacking normal ***p53*** . These results indicate a role for pS3 in the IR pathway, which is completely ***p53*** dependent, and in other genotoxic stress responses, in which ***p53*** has a cooperative effect but is not required.

L10 ANSWER 25 OF 36 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 93248215 MEDLINE
DOCUMENT NUMBER: 93248215 PubMed ID: 8387205
TITLE: Human papillomavirus 16 E6 ***expression*** disrupts the ***p53*** -mediated cellular response to ***DNA*** ***damage*** .
AUTHOR: Kessis T D; Slebos R J; Nelson W G; Kastan M B; Plunkett B S; Han S M; Lorincz A T; Hedrick L; Cho K R
CORPORATE SOURCE: Department of Immunology and Infectious Diseases, Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD 21205.
CONTRACT NUMBER: AI16959 (NIAID) ES05777 (NIEHS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, ***(1993 May 1)*** 90 (9) 3988-92.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930618
Last Updated on STN: 19970203
Entered Medline: 19930601
AB Infection with certain types of human papillomaviruses (HPV) is highly associated with carcinomas of the human uterine cervix. However, HPV infection alone does not appear to be sufficient for the process of malignant transformation, suggesting the requirement of additional cellular events. After ***DNA*** ***damage*** , normal mammalian cells exhibit G1 cell-cycle arrest and ***inhibition*** of replicative DNA synthesis. This mechanism, which requires wild-type ***p53*** , presumably allows cells to undertake DNA repair and avoid the fixation of mutations. We directly tested whether the normal response of cervical epithelial cells to ***DNA*** ***damage*** may be undermined by interactions between the E6 protein ***expressed*** by oncogenic HPV types and wild-type ***p53*** . We treated primary keratinocytes with the ***DNA*** - ***damaging*** agent actinomycin D and demonstrated ***inhibition*** of replicative DNA synthesis and a significant increase in ***p53*** protein levels. In contrast, ***inhibition*** of DNA synthesis and increases in ***p53*** protein did not occur after actinomycin D treatment of keratinocytes immortalized with HPV16 E6/E7 or in cervical carcinoma cell lines containing HPV16, HPV18, or mutant ***p53*** alone. To test the effects of E6 alone on the cellular response to ***DNA*** ***damage*** , HPV16 E6 was ***expressed*** in the carcinoma cell line RKO, resulting in undetectable baseline levels of ***p53*** protein and loss of the G1 arrest that normally occurs in these cells after ***DNA*** ***damage*** . These findings demonstrate that oncogenic E6 can disrupt an important cellular response to ***DNA*** ***damage*** mediated by ***p53*** and may contribute to the subsequent accumulation of genetic changes associated with cervical tumorigenesis.

L10 ANSWER 26 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 15
ACCESSION NUMBER: 1996:542064 BIOSIS
DOCUMENT NUMBER: PREV199699264420
TITLE: Effects of ***DNA*** ***damaging*** agents on gene ***expression*** in two human ***cancer*** cell lines.
AUTHOR(S): Vikhanskaya, Faina (1); D'Incalci, Maurizio; Broggini, Massimo (1)
CORPORATE SOURCE: (1) Inst. Cytol., Russ. Acad. Sci., St. Petersburg Russia
SOURCE: Cellular and Molecular Biology (Noisy-Le-Grand), (1993) Vol. 39, No. 8, pp. 855-862.
DOCUMENT TYPE: Article
LANGUAGE: English
AB In two human ***cancer*** cell lines, the breast mcf-7 and the T-cell leukemia MOLT4, we investigated the cytotoxicity of four antineoplastic agents having different mechanisms of action. We selected doxorubicin as a DNA-topoisomerase II inhibitor, FCE24517 (a Distamycin A derivative) as a DNA minor groove binder with specificity for AT bases, melphalan as an alkylating agent and cis-platinum as an alkylating agent able to form DNA-intrastrand crosslinks. From the cytotoxicity experiments a moderately toxic (less than 10% of growth ***inhibition***) and a highly toxic (about 75% growth ***inhibition***) dose were selected to evaluate the

expression of genes involved in cell proliferation and in cell response to extracellular insults. The ***expression*** was evaluated at early times (60 min.) and 24 hrs. after treatment. At the concentrations utilized in both cell lines we could not find any alteration in the ***expression*** of ***p53*** , gas1 and heat shock 70. After melphalan treatment down regulation of c-myc and of the H2A histone was seen at high doses, while no significant alteration of their ***expression*** was seen with the other drugs.

L10 ANSWER 27 OF 36 MEDLINE
ACCESSION NUMBER: 94011527 MEDLINE
DOCUMENT NUMBER: 94011527 PubMed ID: 8406999
TITLE: Increased accumulation of ***p53*** protein in cisplatin-resistant ovarian cell lines.
AUTHOR: Brown R; Clugston C; Burns P; Edlin A; Vasey P; Vojtesek B; Kaye S B
CORPORATE SOURCE: CRC Dept. Medical Oncology, CRC Beatson Laboratories, Garscube Estate, Bearsden, Glasgow, UK.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, ***(1993 Oct 21)*** 55 (4) 678-84.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19970203
Entered Medline: 19931122
AB We have examined ***p53*** protein levels in cell lines selected for resistance to the chemotherapeutic drug cis-diamminedichloroplatinum (II), cisplatin. The majority of the independent cisplatin-resistant clones isolated by a single selection with cisplatin from the ovarian tumour cell line A2780 showed increased levels of ***p53*** protein compared to the parental cell line. Elevated ***p53*** protein levels were also observed in cisplatin-resistant ovarian human tumour lines isolated after multiple exposures to cisplatin (A2780/cp70 and OVIP/DDP). Direct PCR sequencing of ***p53*** cDNAs showed that both the A2780/cp70 and the parental A2780 cell lines had a wild-type ***p53*** gene sequence. The OVIP and OVIP/DDP lines both had a heterozygous mutation at codon 126. Cell-cycle analysis after gamma-irradiation or cisplatin treatment showed evidence of a G1/S and G2/M cell-cycle checkpoint in both A2780/cp70 and the sensitive parental cell lines. However, the resistant cell line A2780/cp70 showed less ***inhibition*** of DNA synthesis after gamma-irradiation than the sensitive cell line. Transfection of a mutant ***p53*** gene construct (containing a mutation at codon 143, val to ala) into the A2780/cp70 resistant cells conferred a significantly increased sensitivity to cisplatin, suggesting that ***p53*** is a direct determinant of cisplatin resistance in these cells. However, ***expression*** of this mutant ***p53*** in the A2780 cells did not affect sensitivity.

L10 ANSWER 28 OF 36 MEDLINE
ACCESSION NUMBER: 93209539 MEDLINE
DOCUMENT NUMBER: 93209539 PubMed ID: 8384580
TITLE: Wild-type ***p53*** mediates apoptosis by E1A, which is ***inhibited*** by E1B.
AUTHOR: Debbas M; White E
CORPORATE SOURCE: Center for Advanced Biotechnology and Medicine, Rutgers University, Piscataway, New Jersey 08854.
CONTRACT NUMBER: CA53370 (NCI)
SOURCE: GENES AND DEVELOPMENT, ***(1993 Apr)*** 7 (4) 546-54.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930514
Last Updated on STN: 19930514
Entered Medline: 19930429
AB Transformation of primary rodent cells by the adenovirus E1A and E1B oncogenes is a two-step process, where E1A-dependent induction of proliferation is coupled to E1B-dependent suppression of programmed cell death (apoptosis). The E1B gene encodes two distinct transforming proteins, the 19K and 55K proteins, both of which independently cooperate with E1A. E1B 19K or 55K protein, or the human Bcl-2 protein, functions to suppress apoptosis and thereby permits transformation with E1A. The E1B 55K protein blocks ***p53*** ***tumor*** suppressor protein function, indicating that ***p53*** may mediate apoptosis by E1A. In the mutant conformation, ***p53*** blocked induction of apoptosis by E1A and efficiently cooperated with E1A to transform primary cells. When ***p53*** was returned to the wild-type conformation, E1A+ ***p53*** transformants underwent cell death by apoptosis. This induction of apoptosis by conformational shift of ***p53*** from the mutant to the wild-type form was ***inhibited*** by ***expression*** of the E1B 19K protein. Thus, the ***p53*** protein may function as a ***tumor*** suppressor by initiating a cell suicide response to deregulation of growth control by E1A. E1B 19K and 55K proteins provide separate mechanisms that disable the cell suicide pathway of ***p53*** .

L10 ANSWER 29 OF 36 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 16
ACCESSION NUMBER: 1993:166759 BIOSIS
DOCUMENT NUMBER: PREV199395087809
TITLE: Induction of nuclear accumulation of the ***tumor*** -suppressor protein ***p53*** by ***DNA*** - ***damaging*** agents.
AUTHOR(S): Fritsche, Michael; Haessler, Christel; Brandner, Gerhard (1)
CORPORATE SOURCE: (1) Abteilung Virologie, Inst. fuer Medizinische Mikrobiologie und Hygiene der Universitaet, P.O.B. 820, D78 Freiburg Germany
SOURCE: Oncogene, (1993) Vol. 8, No. 2, pp. 307-318.
ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
AB ***Cancer*** therapy drugs, such as diamminedichloroplatinum (cisplatin), mitomycin C, etoposide and a number of other compounds, as well as energy-rich radiation, are known to act on cellular DNA. These agents are shown to induce nuclear accumulation of the so-called ***tumor*** -suppressor protein ***p53*** in fibroblastoid cells, as well as in epithelioid normal and immortalized cells of murine, simian, and human origin. ***p53*** accumulation starts a few hours after treatment and can remain detectable in surviving cells for at least 20 days. Accumulation occurs because of increased ***p53*** protein stability and depends on ongoing translation. It is not the result of enhanced gene ***expression*** . A number of cell cycle inhibitors do not affect ***p53*** protein accumulation, suggesting that the process may start from several points in the cell cycle. Since the increase in the nuclear ***p53*** protein levels occurs within a few hours in most of the treated normal diploid cells, it is unlikely that the accumulated ***p53*** protein is derived from a mutated ***p53*** gene. The results obtained are in accordance with the view that the ***DNA*** ***damage*** -induced ***p53*** accumulation may either ***inhibit*** cell growth, allowing DNA repair process, or, in the case of severe damage, initiate apopotosis.

L10 ANSWER 30 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 17
ACCESSION NUMBER: 94024300 EMBASE
DOCUMENT NUMBER: 1994024300
TITLE: Molecular mechanisms in ***cancer*** induction and prevention.
AUTHOR: Borek C.
CORPORATE SOURCE: Div of Radiation and Cancer Biology, Dept

Radiat Oncol
Tufts Univ Sch Med, and New England Medical Center,Boston, MA 02111, United States
SOURCE: Environmental Health Perspectives, (1993) 101/SUPPL. 3 (237-245).
ISSN: 0091-6765 CODEN: EVHPAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
017 Public Health, Social Medicine and Epidemiology
022 Human Genetics
037 Drug Literature Index
046 Environmental Health and Pollution Control
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Chemical and physical carcinogens, present in our environment and encountered in a variety of occupations, produce damage to DNA. X-rays produce directionizations and indirect hydroxyl radical attack. UV light in the short wavelength is specifically absorbed by unsaturated bonds in DNA, RNA, and proteins. There are a number of genetic sites that are specifically affected by environmental agents, and an increased sensitivity is found in certain genetic diseases. The development of a fully malignant ***tumor*** involves the activation or altered ***expression*** of oncogenes or the inactivation of ***tumor*** -suppressor genes that control normal cellular development. Mutations in the ***p53*** ***tumor*** -suppressor gene are common in diverse types of ***cancer*** and could perhaps provide clues to the etiology of some cancers and to the effect of various environmental and occupational carcinogens in ***cancer*** development. The fact that environmental factors are involved to a great extent in ***cancer*** suggest that ***cancer*** may be preventable. Experimental as well as epidemiological data indicate that a variety of nutritional factors can act as anticarcinogens and ***inhibit*** the process of ***cancer*** development and ***reduce*** ***cancer*** risk. The interaction of cells with a number of environmental and occupational genotoxic substances
such as X-rays, UV light, and a variety of chemicals including ozone results in an enhanced generation of free oxygen radicals and in modified pro-oxidant states. A number of nutritional factors such as vitamins A, C, E, .beta.-carotene, and micronutrients such as selenium act as antioxidants and anticarcinogens. Certain hormones such as thyroid hormones enhance oxidative processes and act as a co-transforming factor in carcinogenesis. A number of bioactive lipids act as ***cancer*** preventive agents. Sphingolipids act on signal transduction pathways and ***inhibit*** protein kinase C and multistep carcinogenesis. Sphingolipids are found in dairy products and milk. .omega.-3 fatty acids suppress X-ray induced transformation as well as promotion. They also ***inhibit*** transformation by the ras oncogene. The .omega.-3 fatty acids act in part by ***reducing*** prostaglandin synthesis. In addition, the ?-3 fatty acids alter the composition of membrane fatty acids that are released from one or more phospholipids, causing remodeling
of cellular phospholipids and ***reduced*** arachidonate-containing species. Such remodeling interferes with transformation.

L10 ANSWER 31 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 18
ACCESSION NUMBER: 92309529 EMBASE
DOCUMENT NUMBER: 1992309529
TITLE: Molecular basis of lymphomagenesis.
AUTHOR: Magrath I.
CORPORATE SOURCE: Lymphoma Biology Section, Pediatric Branch, National Cancer
Institute,Bethesda, MD 20892, United States
SOURCE: Cancer Research, (1992) 52/19 SUPPL. (5529s-5540s).
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
006 Internal Medicine
016 Cancer
022 Human Genetics
025 Hematology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Lymphoid neoplasms, like all malignant tumors, arise as a consequence of
the accumulation, in a single cell, of a set of genetic lesions that result in altered proliferation or increased clonal life span. The most frequently observed genetic abnormalities among the malignant non-Hodgkin's lymphomas are translocations, which appear to be lineage and, to a large extent, lymphoma specific. Recombinases that normally mediate the process of antigen receptor gene rearrangement appear to have
an important (but not exclusive) role in the mediation of these translocations and of other types of gene fusion (e.g., deletion of intervening DNA). Frequently, such fusions result in the increased or inappropriate ***expression*** of crucially important proteins, many of which are transcription factors that regulate the ***expression*** of other genes. These abnormalities, however, do not appear to be sufficient to induce lymphoma, and it is likely that the additional genetic lesions required differ from one ***tumor*** to another. The likelihood of any given clone of cells accumulating a sufficient number of relevant genetic lesions to give rise to a lymphoma is probably a function of its life span. Prolonged survival of a cell clone may be mediated by viral genomes (e.g., Epstein-Barr virus and human T-cell leukemia/lymphoma
virus type 1), by the abnormal ***expression*** of cellular genes that ***inhibit*** apoptosis (e.g., bcl-2), or by the mutation or deletion of cellular genes that are necessary for apoptosis, e.g., ***p53*** . The background rate at which genetic lesions occur is amplified by the interaction of inherited and environmental factors, the latter appearing to be the major determinant of incidence rates. However, inherited factors that influence lymphomagenesis, including variability in the ability to repair ***DNA*** ***damage*** or in the fidelity of antigen receptor recombinases for their signal sequences, may be crucial determinants of which particular individuals in a given environmental setting develop lymphoma.

L10 ANSWER 32 OF 36 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:631200 HCAPLUS
DOCUMENT NUMBER: 117:231200
TITLE: Molecular basis of lymphomagenesis
AUTHOR(S): Magrath, Ian
CORPORATE SOURCE: Pediatr. Branch, Natl. Cancer Inst., Bethesda, MD,
20892, USA
SOURCE: Cancer Res. (***1992***), 52(19, Suppl.), 5529s-5540s
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 73 refs. Lymphoid neoplasms, like all malignant tumors, arise as a consequence of the accumulation, in a single cell, of a set of genetic lesions that result in altered proliferation or increased clonal life span. The most frequently obsd. genetic abnormalities among the malignant non-Hodgkin's lymphomas are translocations, which appear to be
lineage and, to a large extent, lymphoma specific. Recombinases that normally mediate the process of antigen receptor gene rearrangement appear
to have an important (but not exclusive) role in the mediation of these translocations and of other types of gene fusion (e.g., deletion of intervening DNA). Frequently, such fusions result in the increased or inappropriate ***expression*** of crucially important proteins, many of which are transcription factors that regulate the ***expression*** of other genes. These abnormalities, however, do not appear to be sufficient to induce lymphoma, and it is likely that the addnl. genetic lesions required differ from one ***tumor*** to another. The likelihood of any given clone of cells accumulating a sufficient no. of relevant genetic lesions to give rise to a lymphoma is probably a function of its life span. Prolonged survival of a cell clone may be mediated by viral genomes (e.g., Epstein-Barr virus and human T-cell leukemia/lymphoma
virus type 1), by the abnormal ***expression*** of cellular genes that ***inhibit*** apoptosis (e.g., bcl-2), or by the mutation or deletion of cellular genes that are necessary for apoptosis, e.g., ***p53*** . The background rate at which genetic lesions occur is amplified by the interaction of inherited and environmental factors, the latter appearing to be the major determinant of incidence rates. However, inherited factors that influence lymphomagenesis, including variability in the ability to repair ***DNA*** ***damage*** or in the fidelity of antigen receptor recombinases for their signal sequences, may be crucial determinants of which particular individuals in a given environmental setting develop lymphoma.

L10 ANSWER 33 OF 36 MEDLINE
ACCESSION NUMBER: 92323544 MEDLINE
DOCUMENT NUMBER: 92323544 PubMed ID: 1623518
TITLE: Ras-induced hyperplasia occurs with mutation of ***p53***
, but activated ras and myc together can induce carcinoma without ***p53*** mutation.
AUTHOR: Lu X; Park S H; Thompson T C; Lane D P
CORPORATE SOURCE: Department of Biochemistry, University of Dundee, Scotland.
CONTRACT NUMBER: CA-50588 (NCI)
DK-43523 (NIDDK)
SOURCE: CELL, ***(1992 Jul 10)*** 70 (1) 153-61.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920821
Last Updated on STN: 19970203
Entered Medline: 19920811
AB Using a reconstituted mouse prostate organ, the effects on endogenous ***p53*** ***expression*** of the ras oncogene or of the ras + myc oncogenes were investigated. In this system the ras gene alone causes mild hyperplasia, but the combination of ras and myc leads to the formation of carcinomas. Surprisingly, while ***p53*** mutations were found in cells derived from the reconstituted organs containing ras alone, no such mutations were found in the ras + myc-transformed cells. Their growth, unlike that of the cells containing ras alone, was not ***inhibited*** by transfection with plasmids encoding wild-type human ***p53*** . We suggest that ***expression*** of both activated ras and myc genes bypasses the need for ***p53*** mutation by neutralizing the ***tumor*** suppressor activity of normal ***p53*** .

L10 ANSWER 34 OF 36 MEDLINE
ACCESSION NUMBER: 92409653 MEDLINE
DOCUMENT NUMBER: 92409653 PubMed ID: 1528930
TITLE: Molecular alterations in human skin tumors.
AUTHOR: Ananthaswamy H N; Pierceall W E
CORPORATE SOURCE: Department of Immunology, University of Texas M. D.
Anderson Cancer Center, Houston 77030.
CONTRACT NUMBER: R01-CA-46523 (NCI)
T32-CA-09598 (NCI)
SOURCE: PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH,
(1992) 376 61-84. Ref: 131
Journal code: 7605701. ISSN: 0361-7742.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199210
ENTRY DATE: Entered STN: 19921106
Last Updated on STN: 19921106
Entered Medline: 19921022
AB Several genetic alterations that perturb normal cellular growth control mechanisms can cause cancers. These include point mutations, deletions, translocations, amplifications and gene rearrangements and occur primarily in two classes of interacting genes, oncogenes and ***tumor*** suppressor genes. While mutation or amplification of certain oncogenes can facilitate cell growth and ***tumor*** formation (Bishop, 1983, 1991; Hunter, 1991; Land, et al., 1983), loss or mutation of ***tumor*** suppressor genes, which normally ***inhibit*** these processes, can promote ***tumor*** formation (Knudson, 1985; Cavenee, et al., 1989; Marshall, 1991). Human skin tumors display multiple genetic alterations such as Ha-ras gene mutation and LOH, N-ras gene amplification, and mutations in ***p53*** ***tumor*** suppressor gene. In most cases, the mutations in ras and ***p53*** genes are localized to pyrimidine-rich sequences, particularly C-C sequences, which indicates that these sites are probably the targets for UV-induced ***DNA*** ***damage*** and subsequent mutation and transformation. Since UV radiation in sunlight is an environmental carcinogen it is important to understand the molecular mechanisms by which UV radiation induces human skin cancers. In addition, suitable animals models are available for comparative studies and risk assessment. By comparing the various genetic alterations detected in sunlight-induced human skin tumors with those present in UV-induced murine skin tumors, it may be possible to identify the carcinogen-related events that are involved in the multi-step process of carcinogenesis. Studies addressing these issues should provide further insights into the molecular mechanisms of UV carcinogenesis.

L10 ANSWER 35 OF 36 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 92034762 MEDLINE
DOCUMENT NUMBER: 92034762 PubMed ID: 1933891
TITLE: Participation of ***p53*** protein in the cellular response to ***DNA*** ***damage*** .
AUTHOR: Kastan M B; Onyekwere O; Sidransky D; Vogelstein B; Craig R W
CORPORATE SOURCE: Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.
CONTRACT NUMBER: CA 09071 (NCI)
CA 43460 (NCI)
SOURCE: CANCER RESEARCH, ***(1991 Dec 1)*** 51 (23 Pt 1) 6304-11.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199112
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 19970203
Entered Medline: 19911216
AB The ***inhibition*** of replicative DNA synthesis that follows ***DNA*** ***damage*** may be critical for avoiding genetic lesions that could contribute to cellular transformation. Exposure of ML-1 myeloblastic leukemia cells to nonlethal doses of the ***DNA*** ***damaging*** agents, gamma-irradiation or actinomycin D, causes a transient ***inhibition*** of replicative DNA synthesis via both G1 and G2 arrests. Levels of ***p53*** protein in ML-1 cells and in proliferating normal bone marrow myeloid progenitor cells increase and decrease in temporal association with the G1 arrest. In contrast, the S-phase arrest of ML-1 cells caused by exposure to the anti-metabolite, cytosine arabinoside, which does not directly damage DNA, is not associated with a significant change in ***p53*** protein levels. Caffeine treatment blocks both the G1 arrest and the induction of ***p53*** protein after gamma-irradiation, thus suggesting that blocking the induction of ***p53*** protein may contribute to the previously observed effects of caffeine on cell cycle changes after ***DNA*** ***damage*** . Unlike ML-1 cells and normal bone marrow myeloid progenitor cells, hematopoietic cells that either lack ***p53*** gene ***expression*** or overexpress a mutant form of the ***p53*** gene do not exhibit a G1 arrest after gamma-irradiation; however, the G2 arrest is unaffected by the status of the ***p53*** gene. These results suggest a role for the wild-type ***p53*** protein in the ***inhibition*** of DNA synthesis that follows ***DNA*** ***damage*** and thus suggest a new mechanism for how the loss of wild-type ***p53*** might contribute to tumorigenesis.

L10 ANSWER 36 OF 36 MEDLINE
ACCESSION NUMBER: 90297884 MEDLINE
DOCUMENT NUMBER: 90297884 PubMed ID: 2193649
TITLE: Cellular and molecular biological aspects of human bronchogenic carcinogenesis.
AUTHOR: Willey J C; Harris C C
CORPORATE SOURCE: Division of Cancer Etiology, National Cancer Institute,
National Institutes of Health, Bethesda, Maryland.
SOURCE: CRITICAL REVIEWS IN ONCOLOGY/HEMATOLOGY, ***(1990)***

10 (2) 181-209. Ref: 244
Journal code: 8916049. ISSN: 1040-8428.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900907
Last Updated on STN: 19900907
Entered Medline: 19900808

AB This is a time of rapid progress in the field of human bronchogenic carcinogenesis due to recent advances in cellular and molecular biology. Important developments over the last 10 years include establishment of methods for culturing NHBE cells under defined conditions, and molecular biological and biochemical epidemiological techniques for identifying genetic changes that are associated with malignant transformation of these cells. Most progress in defining genes associated with human carcinogenesis has been due to discoveries related to oncogenes and more recently, ***tumor*** suppressor genes. As was described in Section II.B.3.a, we now know that oncogene products serve as growth factors, growth factor receptors, and cytosolic and nuclear regulatory proteins. In addition, although the actions of putative ***tumor*** suppressor genes are less well understood, the first isolated ***tumor*** suppressor gene Rb, interacts with the products of DNA viruses which, in turn, are involved in regulation of transcription as was described in Section II.B.3.b. Thus, not surprisingly, both oncogenes and ***tumor*** suppressor genes code for classes of proteins that are known to play an important role in regulation of cell proliferation. Recently, a second gene that appears to possess ***tumor*** suppression activity (***p53***) has been identified on the short arm of chromosome 17 (17p).

The initial data suggesting a possible ***tumor*** suppressor gene on chromosome 17p came from cytogenetic and RFLP studies associating loss of heterozygosity in the chromosome 17p13 region with ***tumor*** cells and tissues. Since the ***p53*** gene is located in this region it was evaluated and found to be frequently or always altered in several types of ***tumor*** cells. Recently, it was determined that introduction of the wild-type ***p53*** gene into NIH3T3 cells will ***inhibit*** subsequent malignant transformation. Thus, the preponderance of evidence now supports the hypothesis that while mutated ***p53*** acts as an oncogene, the wild-type ***p53*** gene codes for a ***tumor*** suppressor function. The role of balance between oncogenes and ***tumor*** suppressor genes in control of proliferation is presently an active area of investigation. As discussed, introduction of a chromosome containing a ***tumor*** suppressor gene will suppress tumorigenicity of a malignant cell line, even though that cell line possesses an active c-Ha-ras oncogene. Whether or not the level of ***expression*** of an activated oncogene is related to tumorigenicity is presently being investigated.(ABSTRACT TRUNCATED AT 400 WORDS)